Université de Montréal

Le caractère adaptatif du cerveau âgé sain dans le maintien des habiletés du traitement lexico-sémantique : une approche neurofonctionnelle

par Ikram METHQAL

Département des sciences biomédicales
Faculté de Médecine

Thèse présentée
en vue de l'obtention du grade de Philosophiae doctor - Doctorat (Ph.D.)
en sciences biomédicales
option sciences du vieillissement

Mai, 2018

Résumé

La majorité des modèles neurocognitifs expliquant les mécanismes de réorganisation neurofonctionnelle sous-jacents au maintien de la performance cognitive au cours du vieillissement souligne une implication accrue des régions frontales, plus généralement assimilées au contrôle exécutif, et ce dans les domaines les plus sensibles au déclin avec l'âge. La compréhension de ces mécanismes adaptatifs peut être complétée par l'exploration de l'un des domaines les mieux préservés de la cognition, celui du langage, notamment dans ses aspects lexico-sémantiques. L'objectif de cette thèse est d'explorer les mécanismes de réorganisation neurofonctionnelle sous-jacents au maintien des habiletés du traitement sémantique des mots au cours du vieillissement sain.

En s'inscrivant à l'intérieur d'une approche comportementale et neurofonctionnelle, trois études ont été conduites dans le présent travail de recherche par le biais de deux tâches, une tâche de fluence verbale (étude 1) et une tâche catégorisation sémantique (études 2 et 3) lesquelles requièrent la mise en jeu des processus exécutifs de maintien et de changement.

La première étude démontre, chez l'adulte âgé, une réorganisation stratégique associée à une réorganisation neurofonctionnelle adaptative au niveau des régions temporales et frontales dépendamment des processus stratégiques engagés lors de la production des mots. La seconde étude met en évidence des mécanismes de réorganisation neurofonctionnelle influencés par l'âge mais également par les caractéristiques du profil exécutif, opérant au-delà des régions frontales. Finalement, la troisième étude, axée sur l'analyse des aspects sémantiques en fonction du degré de contrôle requis lors du maintien d'un lien sémantique démontre, qu'au cours du vieillissement, des adaptations neurofonctionnelles permettent le maintien des habiletés de traitement sémantique des mots, ceci variant selon la nature de la tâche, les caractéristiques du profil cognitif, ainsi que selon le degré de contrôle requis lors du traitement sémantiques des mots.

À la lumière de ce travail de recherche, le vieillissement apparait empreint d'un caractère dynamique, adaptatif et évolutif, lequel permet le maintien des habiletés de traitement sémantique des mots dans des tâches langagières, haut niveau, de production orale et de compréhension de mots.

Mots-clés : imagerie par résonance magnétique fonctionnelle, processus stratégiques, traitement sémantique des mots, vieillissement sain, réorganisation neurofonctionnelle, fluence verbale, catégorisation sémantique, contrôle exécutif.

Abstract

Most neurocognitive models that explain how neurofunctional reorganisation supports cognitive performance during aging emphasize the increased involvement of frontal regions, generally known to support executive control, in domains most sensitive to decline with age. An understanding of these adaptative mechanisms can be completed by exploring one of the most well-preserved domains of cognition: that of language, notably in its lexico-semantic aspects. The objective of this thesis is to explore the mechanisms of neurofunctional reorganization underlying the maintenance of semantic word processing abilities during healthy aging.

A behavioral and neurofunctional approach to the current study resulted in three studies being conducted, through two principal tasks: a verbal fluency task (study 1) and a semantic categorisation task (studies 2 and 3), both of which required involvement of the executive functions of maintenance and change.

The first study demonstrates a strategic reorganisation in the older adult, associated with a neurofunctional adaptive reorganisation at the level of temporal and frontal regions, depending on the strategic processes engaged during word production. The second study highlights mechanisms of neurofunctional reorganisation influenced by age but equally so by characteristics of the executive profile, operating beyond the frontal regions. Finally, the third study, which analyses semantic aspects in relation to the degree of control required in maintaining a semantic link, shows that, during aging, neurofunctional adaptation permits the maintenance of the ability to semantically process words, this adaptation varying according to the nature of the task, the cognitive profile characteristics, as well as to the degree of control required during semantic processing.

In light of the present research, aging appears to be imbued with a dynamic character, adaptive and evolutionary, which permits the maintenance of semantic processing abilities for words in high-level language tasks, of oral production, and of word comprehension.

Keywords : functional magnetic resonance imaging, strategic processes, semantic word processing healthy aging, neurofunctional reorganization, verbal fluency, word-matching, executive control.

Table des matières

Liste des tableaux

CHAPITRE III : ARTICLE 1

CHAPITRE IV : ARTICLE 2

CHAPITRE V : ARTICLE 3

Liste des figures

CHAPITRE III : ARTICLE 1

CHAPITRE IV : ARTICLE 2

CHAPITRE V : ARTICLE 3

Liste des abréviations

AG : Angular Gyrus

ANOVA: ANalysis Of VAriance

BA: Brodmann Area

BET : Brain Extraction Tool

BOLD: Blood Oxygen Level Dependent

CRUNCH: Compensation-Related Utilization of Neural Circuits Hypothesis

DLPFC : DorsoLateral PreFrontal Cortex

FA : Fractional Anisotropy

FEAT : FMRIBs Easy Analysis Tool

FOV : Field Of View

FWHM : Full Width at Half Maximum

FILM : FMRIB's Improved Linear Model

FLAME : FMRIB's Local Analysis of Mixed Effects

fMRI: functional Magnetic Resonance Imaging

FSL : FMRIB Software Library

GLM : General Linear Model

HAROLD: Hemispheric Asymmetry Reduction in OLDer adults

HRF: Hemodynamic Response Function

IRMf : Imagerie par Résonance magnétique fonctionnelle

McFLIRT : Motion Correction Linear Image Registration Tool

MRI : Magnetic Resonance Imaging

MMSE: Mini Mental State Examination

MNI: Montréal Neurological Institute

MoCA : Montreal Cognitive Assessment

NSCV : NeuroSciences Cognitives du Vieillissement

PASA: Posterior-Anterior Shift in Aging

PFC Prefrontal Cortex

ROI: Region Of Interest

SCCs : Subjective Cognitive Complaints

SCD : Subjective cognitive decline

SEM : Standard Errors Mean value

SMA : supplementary motor area

SPSS : Statistical Package for the Social Sciences

STAC : Scaffolding Theory of Aging and Cognition

STM : Short Term Memory

TE Time to Echo

TR Time to Repeat

VF Verbal Fluency

VLPFC : VentroLateral Prefrontal Cortex

WAIS : Wechsler Adult Intelligence Scale

WCST Wisconsin Card Sorting Test

À Ma sœur Fatima-Zahra
À Mes parents Najib &
Oumhani

‘’Tenter, braver, persister, persévérer, être fidèle à soi-même, prendre corps à corps le destin, étonner la catastrophe par le peu de peur qu’elle nous fait, tantôt affronter la puissance injuste, tantôt insulter la victoire ivre, tenir bon, tenir tête; voilà l’exemple dont les peuples ont besoin, et la lumière qui les électrise ‘’.
Victor Hugo

Remerciements

Je souhaiterais tout d'abord remercier mon directeur de thèse, D^r Yves Joanette, d'avoir rendu possible ce projet doctoral, de m'avoir guidé tout au long de mon parcours et pour avoir soutenu ce travail de recherche dans les moments les plus difficiles. Merci, pour tout ce que vous m'avez appris, scientifiquement et personnellement. Merci de m'avoir confronté à mes faiblesses, mes forces, de m'avoir permis d'évoluer. Au-delà de cela, votre passion saine et pondérée pour la recherche qui est en constante congruence avec vos valeurs, votre humilité intérieure qui interroge la superficie des choses et se joint à votre auguste charisme témoignent de cet attachement flexible qui rend le travail avec vous facile et agréable. Un grand sage a dit un jour ‘’nous méritons toutes nos rencontres. Elles sont accordées à notre destinée’’. Cher Professeur, je souhaite vous témoigner mon plus grand respect, mon immense estime et ma gratitude la plus sincère.

Je voudrais remercier les membres de mon jury de thèse, pour avoir accepté de faire partie de ce jury. Je les remercie tous les quatre pour le temps qu'ils ont consacré à la lecture du manuscrit et d'avoir apporté leurs connaissances.

Je tenais à remercier Oury Monchi, d’avoir accepté de collaborer activement et généreusement aux premières prémices d’idées qui ont fait naitre ce projet.

Je souhaite remercier chaleureusement, Maximilliano Wilson, pour avoir largement contribué à l'élaboration de ce travail ! Merci pour tes judicieux conseils et ta grande bienveillance qui pousse à voir le fond des choses sans craindre le moindre doute. Merci, simplement pour avoir été là !

Je souhaite adresser toute ma gratitude à mon cher ami Michael, mon ange-gardien ! Tu as été toujours présent à mes côtés tant pour les beaux que les mauvais moments. Je te remercie pour la disponibilité dont tu as fait preuve - pris sur ton temps personnel, même les fins de semaine - pour ta patience, pour tes corrections et tes relectures méticuleuses et surtout pour ton écoute attentive. Tu es ce petit frère que j’ai toujours souhaité avoir. Tu as supporté et enduré mes doléances interminables sans jamais rien reprocher ou juger. Ta générosité et ta prévenance sont les témoins de l’homme de valeur et intègre que tu représentes à mes yeux. Je te dois beaucoup mon adorable Ami ! Te connaitre est un vrai privilège que la vie m’a accordé.

Des remercienments pleins de tendresse à Audrey et Louise, mes adorables bibliothécaires du CRIUGM. Nos discussions interminables sur la politique et l’éducation vont me manquer terriblement. Merci d’avoir rendu mes périodes de rédaction agréablement supportables.

Merci à mes amis (e) et collègues du CRIUGM pour vos encouragements, votre gentillesse, et votre patience durant les périodes creuses qui ont parsemé ce parcours. Je pense en particulier à Perrine d’avoir été présente depuis les débuts et d’avoir fait preuve d’un soutien indéfectible, sincère, spontané et inconditionnel, à Edith pour sa belle énergie et sa joie de vivre, à Thanya pour sa tendresse et sa gaieté de coeur, à Mahnoush pour son support, à Anaïs pour sa générosité de cœur et son affection et à Pierre pour ses judicieux conseils. À Basile P., merci d'avoir voulu partager avec moi une partie de ton immense savoir, merci pour ta rigueur scientifique, ta grande générosité et ton apport inquantifiable à ce travail. Merci d'avoir gardé toujours ta porte ouverte pour acceuillir mes multiples interrogations à des moments très critiques. À Audrey avec qui j'ai ratissé salles de cinéma, de théatre et de concert. Merci d'avoir fait réactiver ma vie sociale. Merci pour les moments de rigolades complices. À vous tous, merci pour votre enthousiasme naturel et l'énergie positive que vous avez pu m'insuffler chaque jour durant ces dernières années.

Merci à mes amis(e) et collègues de l'HRVM pour leurs encouragements. Je pense en particulier à notre petite équipe de psychologues au grand cœur. J'exprime ma très profonde reconnaissance à Yves G. pour avoir suivi et révisé très régulièrement et si méticuleusement mon travail. J'ai toujours trouvé tes conseils très judicieux dans chacune des étapes de mon travail. Je ne pourrai jamais assez te remercier pour ton support inconditionnel et constant. Merci à Annick S. pour son support moral et Coline PM pour sa belle générosité d'âme. À ma collègue neuropsychologue (Marie-Thérese) avec qui j'ai partagé tant de moments de rire et de doutes et qui a su m'insufler le courage et la confiance nécessaires pour m'affranchir des obstacles. À mes collègues du service social (Vanessa P., Valérie B., Nathalie R., Louise C., Stéphanie G. et Claudine B.) pour m'avoir écoutée durant des heures et m'avoir toujours encouragée à persevérer. À ma grande Amie Diane C., aucun mot ne peut exprimer la tendresse et l'affection que j'ai pour toi. Merci de m'avoir toujours accompagné, épaulé et soutenu à des périodes différentes de mon parcours doctoral. À l'équipe de physiothérapeutes (Aurélie, Camille, Annie et les deux Gabrielle) et d'ergothérapeutes (Angela, Marie-Pierre, Brenda et Josée) qui m'extirpaient de mes longues et interminables périodes d'écriture pour partager avec elles des moments de rire et de détente. À Marie-Jo et sa terrasse de Ville-Marie. À Mélissa pour avoir aménagé mes horaires de travail durant mes périodes de rédaction.

Je tiens également à remercier tous les participants, pour le temps qu'ils m'ont accordée. Sans eux ce projet n'aurait jamais pu aboutir.

Merci à l'exceptionnelle équipe du service informatique du CRIUGM (Johane, Dominique, Derek) d'avoir facilité l'accomplissement de ce projet. Vous êtes cette âme chaleureuse qui caractérise tant notre centre de recherche. Mille fois merci ! Ma chère Johane L., je ne saurais manquer d'exprimer toute ma gratitude pour m'avoir accompagnée jusqu'au bout de cette aventure.

À Ma grande sœur Fatima-Zahra, mon guide ! Tu as fortement influencé mon parcours universitaire et professionnel. Je te remercie pour tout ce que tu m'as appris. Merci d'avoir toujours demeuré à mes côtés, de n'avoir JAMAIS douté en mes capacités à relever les plus grands défis, de m'avoir poussée à aller toujours plus loin, d'avoir toujours cru en moi, d'avoir chéri, aimé, rassuré et protégé ta petite sœur inconditionnellement. Quelle chance de t'avoir comme grande sœur, quel honneur et privilège de t'avoir dans ma vie. Je t'aime à l'infini ma sis' adorée, tu as su me guider avec beaucoup de tendresse et d'affection. Je t'admire tant ! Je te dois tant ! Te voilà encore une fois à mes côtés pour clore un chapitre de mon parcours de vie.

Merci, merci et encore merci à mes adorables parents, Najib et Oumhani pour m'avoir fait comprendre à leur façon que les choses les plus importantes de la vie se trouvent ailleurs. De m'avoir permis d'arriver jusque là, pour vos sacrifices et votre tendresse sans limite et sans condition. Je vous serai éternellement reconnaissante d'avoir toujours été là à mes côtés malgré la distance et les réunions familiales restreintes. Mes chers parents, je vous aime du plus profond de mon cœur ! Merci de m’avoir inculquée les vraies valeurs qui ont fait de moi la personne que je suis. Ce travail est en grande partie pour vous.

INTRODUCTION

Pour la première fois dans l'histoire, les projections démographiques montrent que l'espérance de vie d'environ un Canadien sur quatre sera supérieure à 65 ans. D'ici à 2040, l'Organisation mondiale de la Santé s'attend à ce que la proportion des aînés âgés de 80 ans et plus connaisse une croissance exponentielle. Aujourd'hui plus que jamais, la nécessité d'une autre approche du vieillissement cérébral et cognitif est de plus en plus reconnue alors même qu'une approche réductrice axée sur le déclin s'est longtemps imposée dans les études sur le vieillissement cognitif sain.

Faisant historiquement suite au développement des recherches en psychologie cognitive du vieillissement, l'avènement des techniques de neuroimagerie fonctionnelle a largement contribué à l'émergence d'un nombre sans cesse croissant d'études qui envisagent le vieillissement sous l'angle des neurosciences cognitives. Parallèlement à cette nouvelle approche spécifique du vieillissement, l'observation des corrélats neurofonctionnels des différences d'âge dans des domaines cognitifs sensibles à l'avancée en âge a permis la conceptualisation de différents modèles neurocognitifs, lesquels ont forgé une vision du vieillissement résolument positive. En outre, grâce à l'impulsion reçue par la convergence relative des données empiriques, les études en neurosciences cognitives du vieillissement ont permis d'isoler un caractère adaptatif et dynamique mais indubitablement complexe et hétérogène du vieillissement neurocognitif.

Bien que le maintien relativement tardif du langage au cours du vieillissement ne fasse plus débat, les modifications de l'activité cérébrale qui y sont associées sont très peu explorées. D'ailleurs, l'intégration des modèles neurocognitifs du vieillissement aux études sur les activations cérébrales observées chez l'adulte âgé lors des tâches langagières, ont conduit à des résultats parfois contradictoires par rapport à la signification des changements neurofonctionnels au sein des régions frontales, lesquelles sont généralement associées au fonctionnement exécutif. En effet, l'avantage de ces ressources exécutives pour la performance de l'adulte âgé aux tâches langagières de compréhension et de production demeure incertain et controversé (Diaz, Rizio, & Zhuang, 2016).

Une telle constatation souligne l'intérêt de prendre en compte l'hétérogénéité des trajectoires cognitives au cours du vieillissement pour mieux appréhender la signification des manifestations neurofonctionnelles et ainsi éviter une exploration plus parcellaire du cerveau âgé restreinte à l'étude des fonctions de manière isolée. D'ailleurs, malgré des trajectoires développementales séparées par lesquelles le langage, dans ses aspects lexico-sémantiques, et le contrôle exécutif évoluent, leur interdépendance est clairement bien établie et conséquemment déterminante et substantielle pour toute performance de traitement sémantique des mots.

Plus particulièrement, de par l'organisation du stock sémantique, la manipulation flexible des connaissances sémantiques est tributaire de la mise en jeu efficace des processus exécutifs de maintien (stratégie d'exploitation) et de changement (stratégie d'exploration), deux composantes du contrôle exécutif indissociables de la fonction langagière et par conséquent déterminantes pour toute performance de traitement sémantique. En outre, de par l'observation des soubassements neuroanatomiques du traitement sémantique des mots, l'interdépendance avec les régions responsables du contrôle exécutif se révèle mieux établie. À notre connaissance, aucune étude, s'inscrivant à l'intérieur d'une approche comportementale et neurofonctionnelle, ne s'est intéressée, jusqu'à présent, aux mécanismes de réorganisation neurofonctionnelle sous-jacents aux processus exécutifs du traitement sémantique des mots au cours du vieillissement sain.

Ce travail de recherche est organisé en trois parties principales, soit une section théorique, une section consacrée aux trois études puis d'une dernière section comprenant une discussion et une conclusion générale.

La section théorique est divisée en deux chapitres : ***Le premier chapitre*** sera consacré à une présentation des principaux modèles théoriques du vieillissement cognitif ainsi qu'à la contribution des neurosciences cognitives à la compréhension du caractère adaptatif du vieillissement neurofonctionnel. Ce chapitre aura pour objectif de souligner l'implication de la vision actuelle du vieillissement neurocognitif dans l'établissement des nouvelles frontières des neurosciences cognitives du vieillissement (NSCV). ***Le deuxième chapitre*** soulignera les travaux en NSCV ayant participé à la compréhension des phénomènes de réorganisation neurofonctionnelle sous-jacents à la préservation relative des habiletés langagières, ceci autant en ce qui a trait à la production que pour ce qui est de la compréhension des mots. Parallèlement, un regard particulier sera accordé aux études ayant porté sur le traitement sémantique des mots. À la suite de ces deux chapitres, *la problématique et les objectifs* de ce travail de recherche seront également présentés.

La section subséquente permettra de rapporter *les 3 études* menées dans le cadre de ce travail de recherche.

La première étude (Article 1) s'intéresse aux changements neurofonctionnels associés aux aspects stratégiques (ou exécutifs) de maintien et de changement mis en place par l'adulte âgé préservant un niveau élevé de performance à une tâche d'évocation lexicale sémantique et orthographique.

La deuxième étude (Article 2) est axée sur *les aspects exécutifs* du traitement lexico-sémantique à l'aide d'une nouvelle tâche de catégorisation sémantique. Cette étude rassemble d'une part les effets de l'âge sur les modifications de l'activité cérébrale lors du maintien ou du changement de règle de catégorisation sémantique et d'autre part la spécificité des phénomènes neurofonctionnels relatifs aux habiletés exécutives chez l'adulte âgé. Cette étude permet de répondre à des questions de recherche complémentaires en faisant appel à l'implication des caractéristiques du profil cognitif au cours du vieillissement comme un facteur supplémentaire déterminant de la réorganisation neurofonctionnelle.

La troisième étude (Article 3) se base sur la même tâche expérimentale, à savoir celle de la catégorisation sémantique, mais elle se focalise plus particulièrement sur *les aspects sémantiques* des règles de catégorisation. Ceux-ci sont envisagés en termes de niveau du contrôle sémantique en lien avec la complexité du traitement du lien lexico-sémantique. Cette troisième étude permet de fournir une meilleure compréhension des changements neurofonctionnels associés au niveau du contrôle sémantique exigé par la tâche de catégorisation en lien avec le maintien des habiletés du traitement lexico-sémantique au cours du vieillissement.

Enfin, la dernière section correspond au chapitre de discussion, qui permettra de confronter les résultats divergents, de même que ceux qui ouvrent une piste intéressante quant à la nature même du caractère adaptatif du cerveau âgé dans le maintien des habiletés lexico-sémantiques, notion défendue dans notre travail. La contribution de notre recherche dans le domaine des NSCV sera ainsi soulignée à la lumière des données comportementales et neurofonctionnelles rapportées, et cela avant de proposer quelques perspectives de recherches puis parvenir à une conclusion générale.

SECTION THÉORIQUE

CHAPITRE I : Nouvelles frontières du vieillissement neurocognitif

Avant de présenter les nouvelles frontières en NSCV, il semble essentiel de retracer le parcours des différentes démarches d'ordre théorique et de recherche qui en ont permis l'émergence. En fait, deux démarches très distinctes, celles de la psychologie cognitive et des neurosciences du vieillissement, ont respectivement développé des modèles divergents relativement aux changements cognitifs et neurofonctionnels ayant cours dans le vieillissement. Ces deux principaux champs de recherche abordaient les changements cognitifs et neuronaux de manière indépendante, voire opposée. En effet, pendant que la psychologie cognitive du vieillissement explorait les effets délétères du vieillissement en s'appuyant sur des mesures comportementales de la cognition, les neurosciences du vieillissement s'efforçaient de préciser les effets du vieillissement sur l'anatomie et la physiologie cérébrale, offrant ainsi une description des modifications cérébrales associées au déclin cognitif. Cependant, les points forts de chaque champ de recherche, lorsque mis en commun, peuvent soutenir une réflexion convergente vers une démarche théorique commune, apte à favoriser l'émergence de nouvelles notions dans la compréhension du vieillissement neurocognitif.

Il parait toutefois que le vieillissement a longtemps et essentiellement été défini en termes de pertes plutôt que gains. À l'intérieur de ce cadre, l'essor des techniques de la neuroimagerie fonctionnelle a permis de faire évoluer les théories cognitives du vieillissement, permettant ainsi de montrer que le déclin cognitif et cérébral, notamment chez les adultes âgés, est marqué par des réorganisations cognitives et neurofonctionnelles impliquant un recours accru aux ressources exécutives. Dans une perspective davantage intégrative et dynamique des modifications neurocognitives, l'avènement *des NSCV* a ainsi permis d'offrir une meilleure compréhension des liens entre les changements neuronaux et de modification de la performance cognitive. Les sections subséquentes vont ainsi aborder *l'évolution* des principaux modèles explicatifs du vieillissement neurocognitif depuis les 30 dernières années et *la (r)évolution* qu'ils ont créée dans l'élaboration des nouvelles frontières du vieillissement neurocognitif. Dans cette première section théorique introductive, une première synthèse soulignera le lien avec le cadre conceptuel du présent travail de recherche.

1.1 Considérations théoriques classiques du vieillissement cognitif

Alors que certains domaines cognitifs semblent être plus affectés par les effets délétères du vieillissement, d'autres demeurent largement intacts. Plus spécifiquement, avec l'avancée en âge, la vitesse de traitement de l'information diminue (Salthouse, 1996), la capacité de la mémoire de travail réduit (Park et al., 1996), le fonctionnement de la mémoire épisodique décline et la capacité d'inhibition de l'information non pertinente devient laborieuse (Lustig, Hasher, Zacks, 2007). Malgré toutes ces pertes inéluctables, les connaissances cumulées sur le monde, le vocabulaire et les connaissances sémantiques demeurent épargnées et peuvent même être enrichies au cours de l'avancée en âge.

Sur la base d'une pertinence théorique bien distincte, l'émergence des hypothèses explicatives du vieillissement cognitif a été marquée par l'élaboration de deux modèles théoriques principaux : 1/ Un modèle à facteur unique s'appuyant sur *une réduction des ressources de traitement* disponibles induisant une diminution des performances dans plusieurs domaines cognitifs ; 2/ Un modèle à deux facteurs rendant compte de la complexité des changements cognitifs en terme d'interaction requise entre plusieurs facteurs pour le maintien d'un fonctionnement cognitif adéquat face aux effets délétères du vieillissement.

1.1.1 Modèle à facteur unique

- Hypothèse de la diminution des ressources de traitement

L'approche à facteur unique se réfère à une cause commune explicative des différences de performance liées à l'âge dont la fonction principale est d'allouer la quantité de ressources nécessaires à l'accomplissement de différentes tâches. La notion de ressources a été conçue en termes de capacité attentionnelle, de vitesse de traitement ou sous forme de capacité exécutivo-frontale. Dans ce contexte, une réduction de ces ressources avec l'âge affectera négativement les capacités cognitives.

- Limitation des ressources attentionnelles, de la mémoire de travail et de l'inhibition.

Modélisée à partir du cadre dissociatif entre intelligence fluide et cristallisée proposé par les travaux de Cattell (1963, cité par Baltes, 1987), *la théorie de la limitation de ressources de Craik & Byrd (1982)* est basée sur l'idée qu'un déclin avec l'âge de certaines fonctions cognitives serait associé à la réduction des ressources attentionnelles nécessaires à l'exécution d'un ensemble d'opérations cognitives. En regard de cette hypothèse, la capacité de traitement de l'information chez l'adulte âgé a été considérée comme inefficiente plutôt que défaillante puisque des ressources attentionnelles suffisantes seraient potentiellement disponibles chez les adultes âgés mais pour certaines raisons, ces ressources ne sont pas mobilisées. De ce fait, les adultes âgés auraient de la difficulté à initier spontanément des stratégies d'encodage ou de récupération efficaces lors d'une tâche de mémoire épisodique verbale. Néanmoins, une amélioration de leurs performances mnésiques est constatée lorsque ces processus sont guidés à l'aide d'un support environnemental (stratégies induites). Par conséquent, le recours à un support environnemental parait en grande partie associé à la réduction des traitements auto-initiés fortement couteux en ressources attentionnelles au cours du vieillissement. Au sens de l'hypothèse de la limitation de ressources attentionnelles, les différences de performance entre jeunes et âgés sont d'autant plus évidentes dans une tâche cognitive complexe nécessitant des opérations auto-initiées, coûteuses en ressources attentionnelles (Craik & McDowd, 1987; Bouaazaoui, Angel, Fay, Taconnat, Charlotte, & Insigrini, 2014 ; Angel et al., 2010). Contrairement aux adultes âgés, le recours à des ressources exécutives lors de la mémorisation des mots est défavorable pour les adultes jeunes. De manière plus intéressante, l'hypothèse défendue par Craik & Rose, (2012) a été confirmée par un ensemble d'études portant sur la mémoire de travail et l'inhibition portant sur l'effet d'une limitation des ressources cognitives sur la diminution de la performance cognitive avec l'âge. Cependant, l'amplitude des effets du vieillissement se retrouve réduite grâce à un recours aux ressources exécutives pour une réalisation efficace de différentes tâches cognitives.

Dans un autre contexte cognitif, moins inattendu pour les recherches menées en psychologie cognitive, Craik & Byrd (1982) ont voulu tester leur hypothèse de limitation de ressources attentionnelles dans un des domaines cognitifs le plus préservé au cours du vieillissement. Leurs travaux ont porté sur la possibilité d'implication des ressources attentionnelles lors de la réalisation des tâches de mémoire sémantique. Par l'entremise d'une tâche d'évocation lexicale phonologique — une catégorie débutant avec une certaine lettre (Fruit — P -> pêche, poire) — et de décision sémantique – juger de l'appartenance catégorielle d'un exemplaire d'une catégorie (Fruit — pomme ou chaise), les auteurs ont rapporté une différence d'âge plus importante lors de l'évocation phonologique qui requiert la mise en jeu de stratégies auto-initiées plus coûteuses en ressources pour les adultes âgés, tandis que lors d'une tâche de décision sémantique plus basée sur des représentations sémantiques, supposée être à un certain degré, en mode plutôt automatique, les différences d'âge sont réduites. De manière générale, leurs résultats plaident en faveur, encore une fois, d'un désavantage des âgés relativement aux jeunes lorsqu'ils doivent se baser sur des stratégies auto-initiées de manière consciente et contrôlée.

- Ralentissement de la vitesse de traitement

La vitesse de traitement est une ressource cognitive globale impliquée dans plusieurs tâches cognitives. *La théorie de ralentissement de la vitesse de traitement de Salthouse (1991b, 1996)* considère le ralentissement cognitif comme un indicateur de la limitation des ressources de traitement de l'information impliqué dans la diminution de la performance cognitive liée à l'âge. Selon Salthouse (1996), le vieillissement cognitif serait le reflet d'un ralentissement de la vitesse de traitement qui médiatiserait le déclin de la performance par le fait que les opérations cognitives ne peuvent pas toutes être menées à leur terme dans le temps imparti (mécanisme de la limitation temporelle), et que le résultat d'une première opération cognitive n'est plus accessible lorsqu'une deuxième opération s'achève (mécanisme de la simultanéité). Par conséquent, ces deux mécanismes qui définissent le ralentissement de la vitesse de traitement au cours du vieillissement semblent contribuer à l'émergence d'une différence de performance liée à l'âge dans une grande variété de tâches cognitives. Malgré le rôle trivial du ralentissement de la vitesse de traitement dans la compréhension globale du déclin cognitif avec l'âge, il en demeure néanmoins partiel dans la considération de la complexité des changements cognitifs qui s'y opèrent.

Dans cette optique, nous pouvons noter qu'un certain nombre d'auteurs se sont opposés à la théorie d'un ralentissement général comme unique cause des effets de l'âge sur la cognition (Greenwood, 2000, 2007). En effet, le vieillissement cognitif ne peut pas être seulement compris grâce à l'addition d'un facteur de ralentissement mais serait proportionnel et dépend du type de tâche et du domaine cognitif envisagé. Cette hypothèse explicative du vieillissement cognitif a inclus récemment la notion de modulation des changements cognitifs en lien avec les processus exécutifs et le degré d'association aux connaissances sémantiques (Salthouse, Pink, & Tucker-Drob, 2008). D'ailleurs, les différentes positions théoriques du vieillissement cognitif se recoupent de plus en plus, avec une approche alternative en adoptant, un point de vue multifactoriel qui considère la prise en compte des ressources de traitement (vitesse de traitement et mémoire de travail) et des connaissances cumulées comme fondamentale pour une meilleure compréhension de la complexité des changements cognitifs et des différences de performances dans le vieillissement (Hedden & Gabrieli, 2004).

Au vu de cette base heuristique construite sur une dimension interprétative de la cognition, les théories cognitives développées en psychologie cognitive du vieillissement admettent l'idée d'une limitation, avec l'avancée en âge, d'un de ces deux types de ressources et ce, qu'elle soit attentionnelle ou en termes de vitesse de traitement. Toutefois, un recours aux ressources exécutives comme un mécanisme de soutien régulateur des pertes cognitives spécifiques au vieillissement cognitif semble aussi être une cause explicative de la variance des performances avec l'âge. Comme on le verra dans les parties subséquentes, cette hypothèse explicative est largement considérée dans les études conduites en NSCV.

- *Hypothèse exécutivo-frontale West (1996)*

L'hypothèse d'un déficit précoce du contrôle exécutif consécutif à une altération des régions frontales a été proposée comme une caractéristique fondamentale à la compréhension du vieillissement cognitif (particulièrement sur la mémoire épisodique). Au regard de cette hypothèse, les premières données de la neuroimagerie ont considéré qu'une altération avec l'âge qui touche préférentiellement le cortex frontal est reflétée par des changements neuroanatomiques et neurochimiques plus marqués que ceux qui surviennent dans les autres régions corticales (pariétales, temporales et occipitales). De façon plus précise, plusieurs données peuvent être mentionnées de ce point de vue. Elles sont relatives au fait que l'on observe une réduction générale du volume cérébral (Raz, 2000), une diminution de la densité synaptique et de la quantité de la substance blanche (Raz, 1998), de même qu'une hypofrontalité dopaminergique (hypothèse de la neuromodulation ; Li, Lindenberger, & Frensh, 2000). La convergence de ces mesures a permis de renforcer l'hypothèse exécutive du vieillissement cognitif comme étant à l'origine des effets de l'âge sur un certain nombre de fonctions cognitives (Raz, 2000 ; Braver et al., 2001). En conséquence, une diminution des performances des adultes âgés à différentes épreuves impliquant le contrôle exécutif a été mise en évidence dans des épreuves de classement de cartes de Wisconsin (Bugg, Zook, Delosh, Davalos & Davis, 2006) qui évaluent les capacités d'abstraction de règles et de catégorisation, des tâches de planification (Tour de Londres, Bugg et al., 2006), ou encore aux épreuves d'évocation lexicale qui nécessitent un maintien et la manipulation de l'information pour faciliter l'accès en mémoire à long terme (Troyer, Moscovich & Winocur, 1997). Néanmoins, la position adoptée par West lors de ces premiers travaux, se retrouve plus pondérée (West, 2000), en précisant que la relation entre la diminution des performances exécutives avec l'âge ne provient pas systématiquement d'un déclin des régions frontales. À cet égard, il a proposé la nécessité de corrélats neurofonctionnels en lien avec un déclin frontal sélectif et la différenciation des processus exécutifs sous-tendus par les structures frontales.

Par ailleurs, étant donné la complexité des tâches exécutives considérées pour apprécier l'intégrité du contrôle exécutif au cours du vieillissement, certains chercheurs ont tenté une spécification des processus exécutifs impliqués et une modélisation de leur fonctionnement.

Plusieurs modèles ont été élaborés, voulant préciser dans un premier temps, si les fonctions qui définissent le contrôle exécutif font partie d'un même système cognitif relativement unitaire ou si elles agissent indépendamment dans leur contribution à la performance aux tâches exécutives. Dans un second temps, ces modèles ont voulu examiner dans quelle mesure les fonctions exécutives peuvent prédire la performance aux épreuves exécutives.

Organisation du système de contrôle exécutif au cours du vieillissement : Évolution homogène ou hétérogène ?

Partant de ces deux conceptions de l'organisation du fonctionnement exécutif (unité ou indépendance de processus) et sur la base de l'hypothèse d'un déficit du contrôle exécutif au cours du vieillissement, des données dans l'ensemble convergentes ont été rapportées dans la littérature. À partir d'analyses factorielles confirmatoires, Miyake et al., (2000) ont apporté plus de clarifications au concept du fonctionnement exécutif, notamment concernant la question portant sur le caractère unitaire ou distinct de processus. À partir d'épreuves évaluant les habiletés exécutives, ces auteurs ont identifié trois processus exécutifs très distincts, essentiels du contrôle cognitif, à savoir l'alternance *(ou shifting)*, définie comme la capacité à modifier une stratégie cognitive lorsque celle utilisée n'est plus appropriée pour la tâche en cours, la mise à jour/maintien (*ou updating*) définie comme la capacité à contrôler l'information entrant en mémoire de travail selon la pertinence pour la tâche en cours et l'inhibition cognitive, définie comme la résistance à l'interférence lorsqu'elle n'est pas pertinente pour l'activité en cours.

Au regard de la modélisation du fonctionnement exécutif proposée par Miyake et al., (2000), un grand nombre de travaux a tenté de déterminer si l'organisation du fonctionnement exécutif observée chez les adultes jeunes conservent la même structure organisationnelle chez les adultes âgés (Adrover-Roig et al., 2012 ; Vaughan & Giovanello, 2010 ; Hedden & Yoon, 2006). Autrement dit, parce qu'un changement de l'organisation du fonctionnement exécutif pourrait intervenir avec l'avancée en âge, quelques arguments pourraient, en effet, être en faveur de l'idée indiquant que des processus exécutifs clairement distincts chez des adultes jeunes auraient tendance à se regrouper et à partager des ressources communes chez les adultes âgés amenant à une réalisation des tâches exécutives de manière différente de celle des adultes jeunes.

Alors qu'un certain nombre de données résultant d'analyses factorielles confirmatoires ont effectivement rapporté une tendance des processus exécutifs à se regrouper lors du vieillissement, en spécifiant la présence d'un seul facteur exécutif (de Frias et al., 2006), d'autres ont proposé un modèle à deux facteurs distincts (mise à jour/alternance et inhibition ; Hedden & Yoon, 2006) ; mémoire de travail/flexibilité et accès à la mémoire à long terme. Une autre étude réalisée par Hull et al., (2008) est parvenue à extraire à partir d'une analyse factorielle confirmatoire, deux facteurs exécutifs distincts (flexibilité et mise à jour) dont la contribution serait plus importante chez les adultes âgés, en plus d'être inversement corrélée. De ce fait, leurs données se trouvent aller à l'encontre de l'hypothèse de dédifférenciation qui prend son origine de l'hypothèse de déclin avec l'âge de la transmission dopaminergique, au niveau des régions frontales, ce qui entrainerait une diminution de la spécificité des traitements et un recrutement de régions cérébrales non spécifiques à la tâche (Li & Lindenberger, 2002). Au-delà de cette interprétation neurofonctionnelle de l'hypothèse de dédifférenciation, une explication d'un point de vue cognitif a été proposée par Antsey, Hofer, & Luszcz, (2003) avec l'idée d'une diminution de la différenciation entre les différents processus cognitifs avec l'âge qui se traduit par une augmentation des corrélations entre les facteurs cognitifs. Autrement dit, le déclin cognitif au cours du vieillissement doit être attribuable à un seul facteur qui en retour augmenterait les corrélations entre les différentes tâches. D'ailleurs, cette hypothèse de dédifférenciation n'a pas été soutenue par les données de Hull, Martin, Beier, Lane, & Hamilton, (2008). Leurs conclusions défendent l'idée selon laquelle la différence d'âge dans les capacités de mise à jour serait une résultante d'une capacité limitée de la mémoire de travail ; nonobstant cette contrainte, un recours plus important des habiletés de mise à jour appert lors de la réalisation des tâches exécutives complexes, supposées requérir plus de ressources, avec pour résultat un niveau de performance globalement équivalent à celui des adultes jeunes. Comme il sera abordé en détails dans les sections subséquentes, les données issues de la modélisation factorielle composée par Hull et al., (2008) concordent avec plusieurs modèles neurocognitifs posant la constatation d'un recours accru aux ressources exécutives pour répondre aux demandes de la tâche au cours du vieillissement.

Bien qu'un nombre d'études aient rapporté à la fois un recouvrement et une séparabilité entre les fonctions exécutives, il apparaitrait qu'un fonctionnement cognitif global de haut niveau chez les adultes âgés soit associé à la présence d'une indépendance des processus exécutifs, bien qu'ils puissent être légèrement inter-corrélés. De manière particulièrement intéressante, de Frias, et al., (2009) ont également testé un modèle à trois facteurs (inhibition, flexibilité et mémoire de travail/mise à jour) chez des adultes âgés. Les résultats indiquent une structure à trois facteurs dans le groupe d'adultes âgés considéré comme le plus cognitivement efficace mais une structure à un facteur chez les autres adultes âgés.

Si les processus exécutifs peuvent être indépendants mais aussi inter-reliés, il en est de même pour leurs soubassements neuroanatomiques (Turner & Nathan Spreng, 2012). Bien que les régions préfrontales et pariétales soient communément activées pour les trois processus exécutifs (alternance, flexibilité et inhibition) chez les adultes jeunes et âgés, une différence d'activation appert selon le processus exécutif envisagé (Collette et al., 2006 ; Braver et al., 2009 ; Herd et al., 2014 ; Kopp, Lange, Howe, & Wessel, 2014). En effet, alors que le processus de mise à jour implique davantage les régions dorsolatérales frontales que les pariétales inférieures, la flexibilité solliciterait les régions pariétales inférieures et le précunéus. Cependant, peu de points de convergence ont été retrouvés parmi les régions cérébrales activées lors de l'inhibition. Cette divergence a été attribuée au caractère insaisissable du processus d'inhibition à travers l'inconsistance des mesures utilisées pour l'évaluer.

En somme, au-delà du fait que des processus exécutifs distincts engagés dans l'analyse des différences d'âge contribuent de manière différente aux tâches cognitives complexes (Bherer et al., 2005 ; De Ribaupierre & Ludwig, 2003), ces derniers partagent entre eux une composante cognitive commune, à savoir la capacité d'exercer un contrôle exécutif nécessaire à la régulation de la dynamique du fonctionnement cognitif (Verhaeghen et al., 2003), et dont les soubassements anatomo-fonctionnels sont relativement distincts mais pas complètement indépendants (Collette & Salmon, 2014). Ce constat semble être retenu par une large variété d'études neurofonctionnelles appuyant l'existence d'un maintien de l'efficacité exécutive avec l'âge concomitante à une réorganisation neurofonctionnelle, laquelle se reflète dans la mise en jeu de processus exécutifs et de régions cérébrales relativement distinctes (Braver et al., 2008 ; Herd et al., 2014). Par conséquent, avec l'avancée en âge, lorsque les ressources disponibles ne sont plus suffisantes, la capacité du contrôle exécutif à gérer l'allocation de nouvelles ressources semble entrainer une évolution moins homogène du système exécutif dépendamment de la composante exécutive impliquée (Adrover-Roig & Barcelò, 2010). Cette capacité à s'ajuster aux demandes de la tâche pour adapter sa réponse laisse supposer la mise en œuvre de stratégies nouvelles rendant les ressources de contrôle cognitif indispensables à la production de réponses adaptées dans une large variété de tâches cognitives. Ainsi, l'identification chez les adultes âgés de profils cognitifs distincts sur un ensemble de critères exécutifs serait potentiellement pertinente pour mieux appréhender les déterminants des mécanismes adaptatifs de la réorganisation neurofonctionnelle qui opèrent au cours du vieillissement.

1.1.2 Modèles duels

Contrairement aux modèles du vieillissement cognitif à facteur unique orientés exclusivement vers les pertes, les modèles duels quant à eux se singularisent par une conception mécanique de la cognition basée sur une distinction entre deux composantes cognitives fondamentales (fluide vs cristallisée de Cattell, 1963 ; mécanique vs pragmatique de Baltes,1987 ; contrôle exécutif vs connaissances de Craik & Bialystok, 2006, 2008) qui évoluent selon des trajectoires de changements bien déterminées au cours d'un parcours de vie. Avec l'avancée en âge, l'aspect évolutif de ce profil duel de la cognition se poursuit par un ajustement continuel entre pertes et gains au moyen d'interactions qui serait un vecteur potentiel de maintien d'un niveau adaptatif de fonctionnement cognitif. Dans cette partie, nous avons choisi de présenter deux modèles duels du vieillissement cognitif, l'un proposé par Baltes & Baltes (1990) et l'autre plus récemment par Craik & Bialystok (2006, 2008) qui seraient le reflet d'un potentiel adaptatif mis en jeu lors du vieillissement. Par conséquent, ces deux modèles théoriques semblent s'accorder avec un large ensemble de données neurofonctionnelles relatives aux recherches menées ces deux dernières décennies en NSCV.

- Modèle de Baltes

La conception du vieillissement cognitif proposée par Baltes & Baltes (1990) se trouve en contradiction avec les premières positions théoriques du vieillissement cognitif mais relativement en concordance avec les modèles neurocognitifs actuels issus des études en NSCV. Dans une perspective dynamique et adaptative, le vieillissement cognitif se définit comme une orchestration continue entre les pertes et les gains qui se traduit par une optimisation des réserves et une réduction des pertes. Malgré le déclin indéniable des ressources fournies par le potentiel biologique au cours du développement adulte, le maintien d'un équilibre fonctionnellement satisfaisant entre gains et pertes contraint l'adulte âgé à recourir de manière plus importante aux ressources dont il dispose. Au regard de ce modèle, cette balance serait donc déterminée par des changements de stratégies qui entraineraient des changements dans les substrats neuronaux responsables du maintien du fonctionnement cognitif.

De manière générale, la perspective de cycle de vie proposée par Baltes & Lindenberger (1997) distingue la mécanique neurobiologique et la pragmatique socio-culturelle comme résultant d'un équilibre dynamique et adaptatif qui opère jusqu'à l'âge adulte. Un tel modèle « bio-culturel » repose sur trois mécanismes distincts : la **S**élection, la **C**ompensation et l'**O**ptimisation, « SOC » qui permettront de « contrecarrer » les effets délétères des pertes liées au vieillissement et de contribuer au maintien des performances cognitives avec l'âge. Selon ce modèle, le processus de *sélection* permet à l'individu de réduire le répertoire des stratégies impliquées dans un domaine cognitif épargné par le déclin précoce lié au vieillissement pour qu'il demeure efficace en fonction des contraintes avec lesquelles il doit composer. Le processus d'*optimisation* se rapporte à la capacité d'adaptation de ces ressources en vue d'atteindre un niveau de performance optimale dans les limites imposées par ses propres ressources. Enfin, si ces deux processus ne suffisent plus, le processus de compensation déterminera l'utilisation des processus ou des habiletés cognitives maintenues ou même améliorées avec l'avancée en âge. Ainsi, l'accumulation des connaissances sémantiques peut contribuer au maintien de la performance cognitive malgré le déclin de certains processus cognitifs qui auraient permis de traiter l'information. Bien que le modèle de Baltes ait été élaboré dans une perspective développementale, il suggère de manière intéressante la présence de mécanismes adaptatifs neurofonctionnels chez l’adulte âgé résultants d’une interaction entre gains et pertes au cours du vieillissement. *Ce modèle théorique est particulièrement intéressant, puisque même s’il n’explique pas les spécificités neurofonctionnelles de ces mécanismes adaptatifs, il semble toutefois être en cohérence avec la majorité des travaux ultérieurs en NSCV, et plus particulièrement avec ceux reflétant des différences d’âge au niveau des corrélats neurofonctionnels.*

- Modèle de Craik & Bialystock (2006)

L’évolution du modèle de Craik du concept limitation de ressources vers une implication respective des représentations et du contrôle cognitif dans différents domaines cognitifs offre l’opportunité d’une meilleure compréhension des changements cognitifs qui accompagnent le vieillissement. Au-delà de cela, les notions véhiculées par Craik et al., (1972 ; 1982 ; 2006) retrouvent leur parallèle dans les récents modèles neurofonctionnels. Par ailleurs, dans ce contexte, les ressources du contrôle exécutif (ou cognitif) seraient des facteurs actifs, déterminants de la performance cognitive au cours du vieillissement.

Le modèle dit duel du vieillissement cognitif tel que proposé par Craik & Bialystok (2006) s’inscrit à l’intérieure d’un cadre conceptuel intégratif décrivant l’idée selon laquelle des aspects adaptatifs associés à l’âge ne peuvent s’observer qu’en considérant l’implication réciproque de deux composantes cognitives fondamentales de la cognition opérant à l’intérieur d’un système collaboratif. Ainsi, *les représentations* correspondraient aux connaissances générales acquises et accumulées tout au long de l’avancée en âge, et resteraient stables au cours du vieillissement ; tandis que *le contrôle exécutif* reposerait sur un ensemble de processus exécutifs (flexibilité, maintien/mise à jour, inhibition) impliqués dans l’habileté à utiliser les connaissances de manière flexible et adaptative mais se trouve contraint au déclin avec l'avancée en âge. De ce fait, l'interaction entre ces deux facteurs déterminants du fonctionnement cognitif constitue une ressource propre qui permet aux adultes âgés de réduire partiellement les pertes et leur assurer une meilleure performance cognitive. Malgré une limitation des ressources touchant certains domaines cognitifs, la position défendue par le modèle duel de Craik s'appuie sur le rôle prépondérant des gains (connaissances) à un moment où les pertes (contrôle exécutif) ne puissent accomplir la tâche cognitive en cours. *Toutefois, les auteurs de cette modélisation duelle du fonctionnement cognitif au cours du vieillissement, assument l'idée de l'interdépendance entre les connaissances et le contrôle exécutif au cours du vieillissement, notamment lorsque des conditions plus coûteuses en ressources nécessiteraient l'implication accrue des processus de contrôle exécutif dans le but d'assurer une bonne efficience comportementale. Par ailleurs, le modèle duel de la cognition de Craik a le mérite de proposer une conception moins parcellaire du vieillissement cognitif restreinte aux pertes comme il sera démontré par les modèles neurocognitifs proposés par les études en NSCV.*

1.2 Modèles neurocognitifs du vieillissement

Durant plusieurs décennies, il y avait peu, voire aucune interaction entre les champs de recherche sur le vieillissement cognitif et les neurosciences. Toutefois, l'avènement de la neuroimagerie fonctionnelle telle que l'Imagerie par Résonnance Magnétique fonctionnelle (IRMf) a apporté des perspectives nouvelles dans les relations entre l'activité cérébrale et le fonctionnement cognitif au cours du vieillissement. Plus important encore, de nouvelles hypothèses et de nouvelles théories ont été proposées pour rendre compte des modifications neurofonctionnelles comme moyen de permettre à l'adulte âgé de maintenir une aptitude cognitive dans un domaine cognitif plus sensible aux effets de l'âge. *Dans les sections* *subséquentes*, nous allons présenter les principaux modèles théoriques du vieillissement cognitif ainsi que ceux issus des études de la neuroimagerie fonctionnelle consacrées aux corrélats neurofonctionnels qui sous-tendent les changements cognitifs au cours du vieillissement. Enfin, dans le cadre de ce travail de recherche, nous synthétiserons les aspects principaux de l'évolution des nouvelles frontières des NSCV.

1.2.1 Réduction de l'asymétrie cérébrale : Modèle HAROLD

Avant l'avènement des techniques de la neuroimagerie fonctionnelle dans les années 1990, le modèle du vieillissement de l'hémisphère droit (Right Hemi-Aging Model; Goldstein & Shelly, 2008) a connu un grand essor dans la compréhension de l'hétérogénéité du déclin cognitif au cours du vieillissement avant d'être confronté à des résultats discordants. Sur la base des données comportementales et non neurofonctionnelles, ce modèle stipule un déclin plus rapide du fonctionnement de l'hémisphère droit avec l'âge par rapport à celui de l'hémisphère gauche. Par conséquent, le déclin des performances dans les épreuves visuo-spatiales — connu pour être principalement dépendantes de l'hémisphère droit — serait plus important que lors d'épreuves verbales. Ce modèle n'a pas été supporté par les études récentes en neuroimagerie fonctionnelle (Dolcos, Rice, & Cabeza, 2002 ; Park et al., 2002). Ainsi, au cours des dernières années, le modèle du vieillissement de l'hémisphère droit a été relativement abandonné en faveur des modèles basés sur une conception fonctionnelle dynamique caractérisée par une augmentation de l'activité cérébrale dans l'hémisphère controlatéral en réponse aux effets délétères du vieillissement. Dès lors, l'exploration de la diminution de latéralisation neurofonctionnelle a commencé à modifier la perception du vieillissement dans son aspect déclinant en proposant d'autres modèles explicatifs des changements neurofonctionnels avec l'âge.

Bien que des preuves évidentes aient plaidé en faveur d'une spécialisation hémisphérique, les travaux de Cabeza, (2001b) défendent l'idée d'une différence dans les profils d'activation cérébrale entre les adultes jeunes et âgés, caractérisés par un recrutement de régions cérébrales controlatérales dans plusieurs domaines cognitifs tels que la mémoire de travail, la mémoire épisodique, l'attention, l'inhibition et la perception. La signification fonctionnelle de ces modifications cérébrales avec l'âge a été conceptualisée par Cabeza dans le modèle HAROLD (*Hemispheric Asymmetry Reduction in OLDer adults*; Cabeza, Anderson, Locantore, & McIntosh, 2002) après avoir pris son origine auprès du modèle de coopération inter-hémisphérique proposé par Banish and Brown, (2000). Ces deux conceptions défendent l'hypothèse selon laquelle la collaboration entre deux hémisphères est plus avantageuse que de recourir à un seul hémisphère en réponse à une charge cognitive élevée. Un ensemble de données convergentes retenues des premiers travaux de Cabeza suggère la tendance des adultes âgés à montrer des activations plus bilatérales au niveau des régions préfrontales là où les jeunes ont des activations plus latéralisées pour effectuer la même tâche. Contrairement au modèle du vieillissement de l'hémisphère droit, le modèle HAROLD suppose que cette réorganisation neurofonctionnelle, peut refléter soit l'utilisation de stratégies cognitives propres à l'adulte âgé (conception psychogénétique) soit le résultat des changements structuraux, qui laisse supposer un recours à des stratégies cognitives semblables aux jeunes mais nécessiteraient un pattern neurofonctionnel plus bilatéral (conception neurogénétique). Ces deux conceptions proposées par Cabeza indiquent une tentative de compréhension des modifications neurofonctionnelles associées au maintien d'un bon niveau de performance cognitive au cours du vieillissement.

Afin de compléter ses résultats, un pas supplémentaire dans la description du modèle HAROLD a été franchi en 2002 par Cabeza. Sur la base d'épreuves de mémoire, il a cherché à comparer le changement de l’activité cérébrale entre deux groupes d’adultes âgés avec un fonctionnement mnésique élevé vs faible et un groupe d’adultes jeunes. Par des mécanismes de réorganisation neurofonctionnelle, il a été suggéré que la réduction de la latéralisation fonctionnelle dans le cortex préfrontal (CPF) avec l’âge devrait être interprétée en termes d’une mise en place de stratégies cognitives distinctes de celles engagées par les jeunes. Sur la base de cette supposition, les adultes âgés avec un fonctionnement mnésique élevé verraient une réduction de leur niveau de performance si les activations au niveau des régions préfrontales controlatérales étant à la base des stratégies cognitives étaient réduites par rapport à celles des jeunes. Paradoxalement, le groupe d’adultes âgés moins performants et le groupe d’adultes jeunes ont présenté un pattern neurofonctionnel plus latéralisé au niveau du CPF gauche tandis que les adultes âgés plus performants ont montré des activations préfrontales plus bilatérales et bénéfiques sur le plan comportemental. Cette conclusion a été rapportée comme une preuve contre l’hypothèse de dédifférenciation fonctionnelle, qui stipule qu’un recrutement bilatéral chez les âgés prédit une difficulté à recruter des régions cérébrales plus spécialisées. Dans le contexte d’une confrontation des deux hypothèses de compensation et de dédifférenciation, il parait toutefois qu’elles ne soient pas complètement contradictoires. D’une part, les auteurs se sont focalisés principalement sur les régions frontales, d’autre part, les corrélats neuronaux avec la performance cognitive associée à l’âge ne semblent pas refléter toute la complexité des changements neurofonctionnels et cognitifs. En d’autres termes, les effets hétérogènes du vieillissement sur le fonctionnement cognitif peuvent inciter à des réorganisations stratégiques spécifiques à des domaines d’expertise. Par exemple, l’augmentation des connaissances avec l’avancée en âge est susceptible de développer une expertise qui conduira à une réorganisation stratégique exigeant moins de ressources et ce, dans le but de maintenir une habileté cognitive

(Angel et al., 2010 ; Hedden & Gabrielli, 2004 ; Troyer et al., 1997). De ce fait, ces adaptations stratégiques qui seront différentes de celles des jeunes sont supposées dépendre de corrélats neurofonctionnels bien distincts chez l'adulte âgé. Cette réflexion sera reprise ultérieurement dans la section discussion et cela à la lumière des résultats issus de notre travail de recherche. Dans l'ensemble, il semble d'ailleurs intéressant de vérifier, d'un point de vue neurofonctionnel, si le phénomène HAROLD peut être observé dans des régions cérébrales au delà du cortex préfrontal ?

1.2.2 Déplacement antéro-postérieur de l'activité cérébrale : Modèle PASA

Un autre modèle des changements de l'activité cérébrale associés au vieillissement est le modèle PASA (pour *Posterior Anterior Shift in Aging*; Davis et al., 2007 ; Dennis & Cabeza, 2008), qui représente une réduction de l'activité cérébrale dans les régions occipito-temporales couplée avec une augmentation dans les régions frontales chez les adultes âgés lors de tâches cognitives. Ce modèle a été décrit par Grady (1994) dans le cadre d'une étude basée sur l'utilisation d'une tâche visuo-perceptuelle. À la suite de ces travaux, le modèle PASA a été reproduit dans un ensemble d'études sur les changements neurofonctionnels avec l'âge, principalement dans des tâches de mémoire de travail (Rypma & D'Esposito, 2000) et de mémoire épisodique (Cabeza et al., 1997a ; Morcom, Good, Frackowiak, & Rugg., 2003). Dans le but de comprendre la signification neurofonctionnelle de ce modèle, deux groupes d'adultes, jeunes et âgés, ont été appariés selon leur niveau de performance en des tâches de perception visuelle et de récupération en mémoire épisodique. Les résultats du pattern de shift antéro-postérieur observé uniquement chez les adultes âgés ont été interprétés comme un effet de l'âge plutôt que celui de complexité de la tâche. Les résultats de l'analyse corrélationnelle entre le changement de l'activité cérébrale et le niveau de performance semblent soutenir l'hypothèse selon laquelle le recrutement accru des régions frontales par les adultes âgés par rapport aux jeunes serait le résultat d'une compensation des déficits visuels sous-tendus par les régions postérieures.

En cohérence avec le modèle PASA, une autre conceptualisation des patterns des modifications de l'activité cérébrale avec l'âge a été proposée par Velanova et al., (2007). Dans le contexte de récupération en mémoire épisodique, les adultes âgés présentent un engagement accru des régions frontales dans les processus tardifs de contrôle de la récupération épisodique tandis que les processus précoces de sélection sont nécessaires pour guider efficacement les processus de récupération chez les jeunes. Ce modèle de déplacement de la charge (*Load-Shift model*) postule une allocation de ressources supplémentaires dans les stades de traitement plus tardifs exigeants en termes de ressources cognitives chez les adultes âgés. Cette idée a été supportée par les travaux de Braver et al., (2003) qui montrent un « shift » dans les stratégies de contrôle cognitif de proactif à réactif. Ces résultats supposent chez les adultes âgés, un bénéfice du déplacement tardif des activations dans des conditions de difficulté élevée, un phénomène qui ne présente pas d'avantage pour les adultes jeunes. Autrement dit, pour répondre efficacement aux exigences d'une tâche cognitive donnée, les adultes âgés tendent à engager de manière tardive les processus cognitifs les plus coûteux en ressources à un moment où la contrainte de leur mise en jeu constitue un avantage indéniable. Cette réorganisation neurofonctionnelle semble cependant particulièrement paradoxale à ce qui était suggéré par d'autres modèles neurocognitifs du vieillissement, à savoir un recours accru aux ressources neurales lors de tâches moins exigeantes cognitivement, mais associées à des domaines cognitifs plus sensibles au déclin avec l'avancée en âge.

1.1. *1.2.3 Hypothèse de compensation associée à l'utilisation des circuits neuronaux : CRUNCH*

Dans une perspective différente, la question des patterns de réorganisation neurofonctionnelle a été abordée dans le cadre de l'hypothèse CRUNCH (Compensation-Related Utilization of Neural Circuits Hypothesis; Reuter-Lorenz et al., 2008). Cette hypothèse repose sur l'effet de la difficulté qui se manifesterait par un recrutement de ressources frontales supplémentaires chez les adultes âgés même en exécutant la tâche à un niveau moindre de difficulté tandis que chez les adultes jeunes engagent ces mêmes ressources mais à un niveau élevé de difficulté. Afin de maintenir un niveau de performance équivalent à celui des jeunes adultes, davantage de ressources sont nécessaires jusqu'à l'atteinte d'une asymptote par les adultes âgés reflétant une limitation des ressources disponibles et une baisse de leur performance face à des demandes plus exigeantes de la tâche. Le compromis réalisé par les adultes âgés entre la limite des ressources disponibles et la performance attendue pour répondre aux exigences de la tâche semblent traduire une saturation du système de traitement, notamment lorsque les ressources exigées par la tâche excèdent leur disponibilité avec pour conséquence une baisse de performance.

Ces conclusions sont conformes à la proposition défendue par Reuter-Lorenz dans le cadre de sa théorie du « *Scaffolding » (Échafaudage en français)* (*Scaffolding Theory of Aging and Cognition* (*STAC*), Park & Reuter-Lorenz, 2009). Selon leur conception, le maintien d'un bon niveau de performance est assuré par un recours à des réseaux neuronaux alternatifs, développés comme une suppléance à ceux devenus moins efficients. En d'autres termes, les patrons de changements neurofonctionnels observés plus particulièrement dans les régions frontales controlatérales, peuvent être modulés par les expériences de vie et le niveau d'expertise, supposés contribuer à la mise en jeu — non arbitraire — de nouveaux réseaux neuronaux pourvoyant à l'adulte âgé des façons alternatives d'exécuter une tâche. Ces facteurs intrinsèques au parcours de vie d'un individu pourraient en fait tout autant influencer la nature des changements neurofonctionnels comme supposée par Reuter-Lorenz et al., qu'à identifier l'existence de processus de réorganisation neurofonctionnelle, au cours du vieillissement, notamment dans le domaine du langage reconnu relativement stables et dont la capacité augmente et/ou s'améliore avec l'accumulation des connaissances acquises et par l'influence grandissante de l'expertise qui en découle. Néanmoins, l'idée d'une réorganisation neurofonctionnelle présumée concomitante à une réorganisation stratégique au cours du vieillissement n'a jamais été explorée dans le domaine du langage.

CHAPITRE II : Neurosciences cognitives du vieillissement et langage

2.1 Apport des modèles neurocognitifs à la compréhension du maintien du langage au cours du vieillissement.

Si la psychologie cognitive a toujours considéré le langage comme l'une des habiletés cognitives de haut niveau longtemps préservée au cours vieillissement, ce n'est que depuis les deux dernières décennies que l'exploration des mécanismes de réorganisation neurofonctionnelle sous-jacents aux différentes composantes langagières (d'abord la phonologie puis la syntaxe et récemment la sémantique) a suscité l'attention des chercheurs en NSCV.

Lorsque les NSCV se sont intéressées aux mécanismes de réorganisation neurofonctionnelle présumés associés au maintien relatif des habiletés langagières, les premiers travaux se sont d'abord orientés vers le langage expressif, pour cause qu'on reconnait une meilleure préservation du langage réceptif. En effet, une performance comportementale équivalente a été retrouvée entre les adultes jeunes et âgés quant à la capacité à juger adéquatement certaines représentations ou concepts sémantiques alors que des différences d'âge ont été rapportées plus particulièrement au niveau des habiletés de production de mots, comme en atteste le phénomène de « mot sur le bout de la langue » (Burke, MacKay, Worthley, & Wade, 1991 ; Thornton & Light, 2006 ; Abrams & Farrell, 2011).

On sait aujourd'hui, que les positions actuelles des recherches en NSCV dans le domaine du langage sont moins tranchées. Au regard des données issues des études en neuroimagerie fonctionnelle, deux hypothèses sur les mécanismes de réorganisation neurofonctionnelle liés à l'âge peuvent être formulées : a) une hypothèse *exécutive* basée sur la relation entre la performance comportementale et la bilatéralisation de l'activité préfrontale ; b) une hypothèse *sémantique* basée sur une implication plus grande des régions temporo-pariétales gauches chez les adultes âgés plus performants. Les conséquences de la réorganisation neurofonctionnelle chez les adultes âgés au niveau des régions préfrontales semblent toutefois plus complexes puisqu'elles peuvent soit interférer avec la performance, soit soutenir davantage la performance des adultes âgés à un niveau comparable à celui des adultes jeunes. À ce jour, très peu d'études ont pu soutenir cette hypothèse dont la plupart portaient sur des tâches de langage peu exigeantes en ressources de traitement. Nous allons dès lors présenter en détails les études relatives à chacune de ces deux hypothèses autant pour les tâches de production que de compréhension

2.1.1 En production

Relativement peu d'études en imagerie par résonance magnétique fonctionnelle (IRMf) ont exploré les changements liés à l'âge dans les patrons d'activation cérébrale qui distinguent les adultes âgés des adultes jeunes lors de la réalisation des tâches de production orale. La plupart d'entre elles ont étudié la signification fonctionnelle de la bilatéralisation du CPF chez les adultes âgés, pour certaines tâches langagières de dénomination d'images (Wierenga et al., 2008), de génération de verbes (Persson et al., 2004), de production de syllabes (Sörös et al., 2011), de jugement de rime (Geva et al., 2012) et de jugement sémantique (Berlingeri et al., 2013). Dans un contexte de changements structuraux, neurofonctionnels et cognitifs, appréhender la relation entre la performance comportementale et de l'activité cérébrale chez l'adulte âgé s'avère dynamique et complexe. D'ailleurs, les études conduites sur le langage expressif ont interprété le recrutement des régions préfrontales additionnelles comme reflétant une augmentation ou une diminution de la performance chez l'adulte âgé.

Lors d'une tâche de fluence verbale (sémantique et phonologique) rythmée par l'expérimentateur (« externally-paced »), Meinzer et al., (2009) ont mis en évidence un recrutement additionnel des régions préfrontales inférieures droites chez les adultes âgés, corrélé négativement avec le nombre de mots produits en fluence sémantique, tandis qu'à performance égale en fluence orthographique dans les deux groupes d'âge, un patron d'activation préfrontale gauche est rapporté lequel était corrélé positivement avec la performance mais uniquement chez les adultes âgés. Dans une autre étude IRMf de Meinzer, Seeds et al., (2012), aux résultats comportementaux similaires, une performance des adultes âgés était positivement corrélée à l'activation dans l'hémisphère droit du CPF inférieur, du cortex frontal supérieur moyen et du cortex temporal moyen en fluence sémantique et du cortex supra-marginal et le cingulaire postérieur en fluence orthographique. Cette augmentation de l'activité préfrontale droite semble s'y associer plus particulièrement à la difficulté à générer un nombre suffisant de mots dans les conditions plus exigeantes[1] en ressources de traitement (Meinzer, Flaish et al., 2012). Tant chez les adultes âgés qu'auprès des jeunes, le recrutement des régions préfrontales controlatérales et la performance comportementale sont négativement plus modulés par les exigences de la tâche de fluence verbale, notamment les critères orthographiques difficiles, que par l'âge. Par ailleurs, en dépit d'un profil de performance similaire en fluence sémantique et orthographique, Marsolais et al., (2014) ont rapporté des patrons d'activations assez comparables entre les adultes âgés et jeunes. Ces résultats recoupent partiellement ceux de Meinzer et al. montrant chez les adultes âgés la présence d'un mécanisme de réorganisation neurofonctionnelle, cependant insuffisant pour améliorer la performance en fluence sémantique et trop faible pour conduire à une baisse de performance en condition orthographique. Dans une étude complémentaire utilisant des mesures hiérarchiques d'intégration fonctionnelle, Marsolais, Methqal, & Joanette, (2015) ont mis en évidence une réduction de la connectivité fonctionnelle

---

[1] Les auteurs ont utilisé quatre tâches de fluence composées de deux niveaux de difficulté (facile vs difficile) pour chaque type de fluence (sémantique vs phonologique). La condition de fluence orthographique difficile était considérée comme l'une des plus difficile des quatre tâches proposées.

chez les adultes âgés en fluence sémantique et orthographique, plus importante au sein du réseau cérébral postérieur par rapport au réseau antérieur (ex. CPF inférieur et supérieur gauches), mais également de manière plus évidente dans le réseau postérieur (cortex angulaire et supramarginal gauche). De plus, cette diminution de l'intégration fonctionnelle modulée par la difficulté des critères de productivité a été plus marquée chez les adultes âgés dans les régions postérieures (p. ex. cortex temporal inférieur gauche) alors qu'un patron neurofonctionnel est observé chez les adultes jeunes dans les régions antérieures (p. ex. CPF inférieur et moyen gauches).

De tels résultats sont en contradiction avec ceux rapportés par Nagels et al., (2012) sur les changements neurofonctionnels associés à une tâche de fluence sémantique réalisée en mode auto-rythmée (« self-paced ») durant des blocs de production très courts (12 s). Ces auteurs ont démontré la présence d'un patron d'activation bilatéral du gyrus temporal supérieur, du cervelet, du gyrus post-central et de l'aire motrice supplémentaire, dans lequel les activations du cortex temporal supérieur droit étaient corrélées négativement avec le nombre de mots produits lors d'une fluence. Les résultats ont démontré qu'une performance plus faible en fluence sémantique résulte d'une activité plus grande du cortex temporal supérieur droit et du cortex frontal supérieur gauche, alors qu'un patron d'activation plus bilatérale du CPF inférieur est corrélé positivement avec l'âge. La portée des conclusions de ces études demeure néanmoins restreinte par les limites des analyses quantitatives associées au nombre de mots produits, alors qu'une analyse qualitative, dont l'interprétation des processus stratégiques auto-initiés lors de productions de mots, permet de contourner ces limites et par conséquent élargie l'observation des mécanismes de réorganisation neurofonctionnelle sous-jacents à la performance comportementale aux tâches de production de mots au cours du vieillissement.

Dans une autre étude IRMf, Wierenga et al., (2008) ont démontré qu'en dépit d'un temps de réponse plus lent en dénomination d'images chez adultes âgés, une performance similaire aux jeunes adultes en termes de réponses correctes était corrélée négativement à une activité frontale accrue et diffuse dans l'hémisphère droit chez les adultes âgés. Or, une variabilité de performance au sein du groupe d'adultes âgés indique que les activations frontales droites chez les adultes âgés moins performants étaient moins avantageuses alors que le profil comportemental et neurofonctionnel inverse a été retrouvé chez les adultes âgés performants. Dans l'ensemble, nous observons globalement que la mise en relation des corrélats neurofonctionnels et de la performance comportementale lors de la production des mots mènent à des interprétations relativement complexes.

2.1.2 En compréhension

Pour tenter de comprendre, d'un point de vue neurofonctionnel, en quoi les modèles neurocognitifs actuels du vieillissement ne peuvent que partiellement appréhender la complexité des trajectoires d'apparition des changements neurofonctionnels, d'autres études ont exploré les corrélats neurofonctionnels des différences d'âge dans les tâches de compréhension, afin d'élargir l'exploration des mécanismes adaptatifs potentiellement présents en dehors des régions frontales.

D'ailleurs, autant pour le maintien des capacités du traitement sémantique que syntaxique au cours du vieillissement (Lacombe et al., 2015 ; Berlingeri, Danelli, Bottini, Sberna, et Paulesu, 2013 ; Tyler et al., 2010), la différence d'âge dans les patrons d'activation est caractérisée soit par une augmentation ou une diminution de l'activité cérébrale, soit par des activations additionnelles dans les régions cérébrales similaires ou différentes de celles recrutées par les adultes jeunes mais observée chez les adultes âgés. D'ailleurs, dans l'étude IRMf de Peelle et al., (2013), des adultes jeunes et âgés devaient effectuer une tâche d'appariement sémantique de mots par leurs attributs (forme ou couleur). Les résultats comportementaux ont démontré une meilleure performance du groupe d'adultes jeunes comparativement au groupe d'adultes âgés. En réordonnant les adultes âgés selon leur performance, puis en les comparant aux adultes jeunes, les résultats IRMf montrent un pattern d'activation temporo-occipital similaire entre les adultes âgés performants et les adultes jeunes. En revanche, les adultes âgés moins performants présentent une diminution de l'activité dans ces mêmes régions et plus spécifiquement dans les régions occipitales. Ces résultats indiquent qu'une augmentation de l'activité occipitale suggère la possibilité d'un recours à des processus stratégiques du traitement visuel efficaces qui améliorent la performance du traitement sémantique chez les adultes âgés performants. Autrement, les auteurs ont comparé les patrons d'activation chez les deux groupes d'adultes âgés. Les résultats révèlent une augmentation dans les régions cérébrales communément recrutées dans le fonctionnement exécutif dont le CPF dorsolatéral et le cortex pariétal inférieur gauche chez les adultes âgés performants en comparaison aux moins performants. Ce patron associé aux processus exécutifs mis en jeu dans le traitement sémantique est sollicité plus efficacement pour supporter le contrôle de l'accès et la manipulation des connaissances conceptuelles. Ainsi, les régions dorsolatérales préfrontales et pariétales inférieures reconnues pour avoir un rôle plus général dans le fonctionnement exécutif s'avèrent représenter une ressource générale mobilisée dans le but de supporter et maintenir la performance de traitement sémantique au cours du vieillissement. Comme le suggère les auteurs, l'observation des changements neurofonctionnels associés à l'âge dans des conditions de traitement sémantique plus exigeantes, autrement dit celles qui nécessitent un degré de contrôle exécutif élevé demeure encore à préciser (Kennedy et al., 2015 ; Hoffman & Morcom, 2017). Dans une étude IRMf sur la compréhension de phrases, Peelle et al., (2010) ont démontré qu'une différence d'âge dans la performance comportementale aux phrases complexes était accompagné d'un recrutement bilatéral plus bénéfique dans l'insula et le CPF inférieur chez les adultes âgés, alors que l'activation du cortex temporal postérieur gauche était quant à elle associée à une moins bonne performance. Deux autres études dans lesquelles une absence de différence de performance comportementale (précision des réponses) entre les deux groupes d'âge (âgés et jeunes) était associée chez les adultes âgés à une bilatéralisation de l'activité dans le réseau fronto-temporale avec un pattern plus diffus dans l'hémisphère gauche pour un traitement syntaxique simple (Tyler et al., 2010) et à un patron bilatéral de l'activité temporale dans des conditions plus complexes (Davis, Kragel, Madden, & Cabeza 2012). En somme, le maintien relatif de la performance chez l'adulte âgé, dans des tâches de production et de compréhension, semble être associé à un recrutement accru des ressources frontales. Ces modifications de l'activité frontale suggèrent une réorganisation neurofonctionnelle chez l'adulte âgé, et ce dans des aires cérébrales impliquées dans des processus du contrôle exécutif (maintien/mise à jour, flexibilité, inhibition…). Par ailleurs, l'interdépendance fonctionnelle entre les régions préfrontales et les aires cérébrales associées (pariétales inférieures et temporales moyennes et inférieures postérieures) soutenue par un ensemble de données de neuroimagerie fonctionnelle issues des tâches sémantiques sollicitant un niveau de contrôle élevé (Binder, Desai, Graves, & Conant, 2009) revêt l'intérêt de questionner les mécanismes adaptatifs de réorganisation neurofonctionnelle sous-jacents aux aspects exécutifs du traitement sémantique au cours du vieillissement.

2.2 Problématique et objectifs de la thèse

Depuis les deux dernières décennies, une approche plus mécanistique du vieillissement neurocognitif a largement contribué à mieux cerner les déterminants des mécanismes de la réorganisation neurofonctionnelle associés au maintien de la performance chez l'adulte âgé dans des domaines cognitifs plus sensibles au déclin. Cependant, l'observation de la signification fonctionnelle des adaptations neurofonctionnelles apparentées à l'un des domaines cognitifs le mieux préservé avec l'âge et plus particulièrement le langage a été *ipso facto* délaissée par les NSCV avant d'être considérée récemment par un nombre très restreint d'études.

À l'intérieur du cadre des modèles neurocognitifs du vieillissement, l'observation des changements neurofonctionnels sous-jacents aux aspects exécutifs du traitement sémantique des mots n'a, jusqu'à présent, jamais été envisagé dans le domaine du langage. Le fait d'y porter intérêt permettra de souligner l'importance de prendre en compte l'interdépendance entre le traitement sémantique et le contrôle exécutif, deux composantes cognitives fondant, d'une part, une meilleure compréhension des changements cognitifs qui opèrent avec l'âge (Craik & Bialystok, 2006, 2008) et déterminante, d'autre part, pour l'efficience de la performance du traitement sémantique (Noonan et al., 2013 ; Withney et al., 2012).

Cette thèse a donc pour objectif principal d'examiner, à l'aide de l'IRMf, les mécanismes de la réorganisation neurofonctionnelle sous-jacents aux aspects exécutifs du traitement sémantique des mots au cours du vieillissement. La portée de cet objectif est ici particulièrement intéressante, d'une part, par le fait que les connaissances sémantiques cumulées avec l'âge et l'expertise susceptible de contribuer à la mise en place spontanée des stratégies cognitives efficientes sont d'autant de preuves en faveur des réorganisations stratégiques supportées par des mécanismes neurofonctionnels adaptatifs. D'autre part, la prise en compte des tâches langagières qui impliquent des conditions de traitement sémantique plus exigeantes, autrement dit celles qui nécessitent un degré de contrôle exécutif élevé est désormais indispensable pour une meilleure compréhension de la complexité des changements neurofonctionnels contribuant au maintien du traitement sémantique des mots au cours du vieillissement. Plus précisément, nous étudions ici, dans deux tâches langagières de haut niveau, les aspects exécutifs du traitement sémantique des mots, que sont le maintien et le changement, deux processus cognitifs déterminants pour la performance sémantique. La première correspond à une tâche de fluence verbale (sémantique et orthographique) *expressive et auto-rythmée*, adaptée à l'IRMf grâce à un design mixte novateur, durant laquelle des adultes âgés performants et des adultes jeunes ont à initier spontanément des processus stratégiques de maintien et de changement. Au cours de la seconde tâche, une tâche de catégorisation sémantique que nous avons élaborée, les deux groupes d'adultes (jeunes et âgés) ont à maintenir un lien sémantique (associé, typique ou atypique) ou à le changer sur la base *de feedbacks* de l'expérimentateur.

CHAPITRE III : ARTICLE 1

More expertise for a better perspective: Task and strategy-driven adaptive neurofunctional reorganization for word production in high-performing older adults

Ikram Methqal[a,b], Yannick Marsolais[c], Maximiliano A. Wilson[d], Oury Monchi[e] and Yves Joanette[a,b]

[a]Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montreal, QC, Canada; [b]Faculty of Medecine, University of Montreal, Montreal, QC, Canada; [c]Centre de Réadaptation en Déficience Physique, Montréal, Canada; [d]Centre de recherche CERVO - CIUSSS de la Capitale-Nationale et Département de réadaptation, Université Laval, Québec, Canada; [e]Department of Clinical Neurosciences, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Canada

Publié dans la revue

Aging, Neuropsychology, and Cognition

Contribution des auteurs

Ikram Methqal: préparation, extraction, analyse et interprétation des données IRMf, comportementales et neuropsychologiques, rédaction du manuscrit

Yannick Marsolais: conceptualisation de l'étude et de la méthodologie, recrutement de participants, expérimentation, contre-cotation des données comportementales, révision du manuscrit

Maximiliano A. Wilson: validation de la méthode de cotation des données comportementales et révision de l'article

Oury Monchi: élaboration du logiciel d'analyse des données IRMf, révision de la méthodologie

Yves Joanette: directeur de recherche, conceptualisation de l'étude et de la méthodologie, interprétation des résultats et révision du manuscrit

Abstract

The suggestion that neurofunctional reorganization may contribute to preserved language abilities is still emerging in aging studies. Some of these abilities, such as verbal fluency (VF), are not unitary but instead rely on different strategic processes that are differentially changed with age. Younger (n = 13) and older adults (n = 13) carried out an overt self-paced semantic and orthographic VF tasks within mixed fMRI design. Our results suggest that patterns of brain activation sustaining equivalent performances could be underpinned by different strategies facing brain changes during healthy aging. These main findings suggest that temporally mediated semantic clustering and frontally mediated orthographic switching were driven by evolutive neurofunctional resources in high-performing older adults. These age-related activation changes can appear to be compatible with the idea that unique neural patterns expressing distinctive cognitive strategies are necessary to support older adults' performance on VF tasks.

1. Introduction

Adaptive aging is a process whereby cognitive performance is preserved through recruitment of appropriate neural resources in response to age-related brain changes, and not the mere maintenance of cognitive processes like those used by younger individuals (Park & McDonough, 2013; Reuter-Lorenz & Cappell, 2008; Stern, 2009). Growing evidence from neuroimaging studies has provided some comprehensive insights into age-related activation differences in some cognitive domains less preserved with age, such as episodic memory (Grady, 1999), working memory (Rypma, Berger, & D'Esposito, 2002), and perceptual processing (Ansado, Monchi, Ennabil, Faure, & Joanette, 2012). With a cognitive neuroscience perspective, the additional recruitment of prefrontal regions in older adults was often reported as the adoption of a cognitive strategy similar to that of younger adults, instead of changes in strategic processes to reach task demands and enhance performance (Cabeza, 2002; Rajah & D'Esposito, 2005; Grady, 2012; Reuter-Lorenz & Lustig, 2005; Reuter-Lorenz, 2002; Cabeza, 2002; Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010; Murray et al., 2015).

However, evidence of the successful bilateral frontal activations has not been consistently reported in healthy aging. In some cases, once older adults were instructed to create an association to deeply encode information, they were still able to carry out an effective strategy that led to success during memory recollection (Grady, 1999; Logan, Sanders, Snyder, Morris, & Buckner, 2002). It would follow that the older adult's processing appears to be simply ineffective rather than completely impaired, since newly acquired externally guided strategies allowed them to maintain performance at a similar level to the younger adult (Craik & Byrd, 1982; Wierenga et al., 2008). However, a simple assumption of higher contribution of prefrontal regions, for a high performance level, seems to be insufficient for capturing the complexity of neurofunctional changes in healthy aging (Greenwood, 2007; Greenwood & Parasuraman, 2010; Morcom & Johnson, 2015; Park & Reuter-Lorenz, 2009), since the engagement of other brain regions began to be considered beyond the prefrontal regions. For instance, Hazlett et al. (1998) showed an age-related activation shift from frontal to occipital regions, invoked to perform a semantic clustering strategy during memory retrieval; this suggests that flexibility in reallocation of neural resources is more beneficial for fulfilling efficient cognitive processes in high-performing older adults.

As many aspects of cognition tend to decline with age, other more knowledge-driven cognitive abilities such as language, vocabulary, and semantic memory – thought to be at the core of knowledge acquisition and experience accumulation – remain relatively stable and may even improve through a life span (Ackerman, 2008; Park et al., 2002; Verhaegen & Poncelet, 2013). Within a context of enhanced life span experience, performance improvement is also attributed to the ability that older adults employed: the implementation of accrued knowledge of specific domains, through an appropriate self-initiated cognitive strategy, all in coping with cognitive ability decline (Bäckman & Dixon, 1992; Hedden & Gabrieli, 2004; Kramer & Willis, 2002; McIntosh et al., 1999; Reuter-Lorenz, 2002; Salthouse, 1988). Such findings inspired the Scaffolding Theory of Aging and Cognition (STAC) proposed by Park and Reuter-Lorenz (2009), which claims that neurofunctional changes observed with age may potentially depend on neural scaffold build-up, based on skills developed through experience in a course of life. These functional manifestations appear to not be exclusively restricted to frontal regions, but reflect differential engagement along brain regions and are useful supports, ostensibly, in the adoption of distinct strategies to provide better performance (Lövdén et al., 2010; Reuter-Lorenz & Cappell, 2008).

Thus, it looks like older adults can display distinct strategies as expressions of trade- offs between cognitive and neural resources changes.

Commonly used as part of the clinical assessment of cognitive and linguistic impairments, verbal fluency has also been effective for drawing lexical exploration and exploitation abilities, based on the production of as many words as possible within a semantic category (e.g., animals) or beginning with a given letter (Bryan, Luszcz, & Crawford, 1997; Delis, Kaplan, & Kramer, 2001; Lezak, Howieson, & Loring, 2004). Numerous studies have argued that both semantic knowledge and executive abilities are involved in semantic and orthographic fluency tasks, at different degrees (Chouiter et al., 2016; Hughes & Bryan, 2002; Hurks et al., 2010; Mayr & Kliegl, 2000; Unsworth, Spillers, & Brewer, 2011). Previous behavioral studies have already reported inconsistent patterns of age-related differences the two fluency tasks in terms of the total of words generated (Ackerman, 2008; Mayr & Kliegl,2000). Indeed, orthographic fluency showed little to no age-related effect, while semantic fluency showed more decline or age stability (Kozora & Cullum, 1995; Marsolais, Methqal, & Joanette, 2015; Meinzer et al.,2009). To more fully understand the discrepancy in verbal fluency performance, some studies dissociated two strategic components, namely clustering (known as exploitation) and switching (known as exploration) to mainly explore the role of these qualitative features in fluency task performance (Parker & Crawford, 1992; Troyer, Moscovitch, & Winocur, 1997). Clustering strategy (or exploitation) is related to the extent of verbal knowledge, while switching strategy (or exploration) depends on executive abilities (working memory and cognitive flexibility). Particularly, for orthographic fluency, a switching strategy is more crucial for high performance due to phonemic variations during the production of words that begin with a certain letter, while semantic fluency promotes a clustering strategy that subserves production within rather broad semantic subcategories (Goñi et al., 2010; Hirshorn & Thompson- Schill, 2006; Raskin, Sliwinski, & Borod, 1992; Troyer, 2000). A comprehensive understanding of the clustering and switching processes underlying a performance of word production includes evidence in favor of the possibility of trade-offs between these two strategic processes, differing as a function of task-goal requirements, yielding efficient performance with age (Hills, Todd, & Goldstone, 2010). For example, the benefit of accumulating knowledge becomes relatively low, older adults may be able to increase exploration even if a situation is more taxing to executive abilities (Mata & von Helversen, 2015). The interplay between changes in some aspects of executive function, and verbal abilities preservation, supports the assumption that older adults can manage these cognitive changes by optimizing a knowledge-driven strategy (Hedden & Gabrieli, 2004; Salthouse, Fristoe, McGuthry, & Hambrick, 1998; Sauzéon et al., 2011; Unsworth et al., 2011). From a neurofunctional point of view, more evidence shows the recruitment of distinct neural substrates in verbal fluency tasks (Destrieux et al., 2012; Henry, Crawford, & Phillips, 2004; Nagels et al., 2012; Tröster et al., 1998). Although numerous neuroimaging findings make claim for frontal involvement in both fluency tasks (semantic and orthographic), they mainly highlight the contribution of temporal regions for semantic verbal fluency. Moreover, to account for discrepancy between performances on fluency tasks, a word retrieval in response to an orthographic criterion appears to depend more on a frontal region-mediated strategic search, while semantic fluency, to an extent, is more dependent on temporal region-mediated semantic memory search (Martin, Wu, Freedman, Jackson, & Lesch, 2003; Mummery, Patterson, Hodges, & Wise, 1996; Robert et al., 1998; Sauzéon et al., 2011). In general, both verbal fluency tasks relied on distinct neural patterns and different uses of strategic processes, which may reflect a differential reliance on executive resources for successful performance during healthy aging.

Hence, verbal fluency tasks represent a reliable paradigm where individual performances can hinge on a self-determined strategy driven by trade-offs between exploitation (or clustering) and exploration (or switching) strategies, depending on task requirement (Hills, Todd & Goldstone, 2010; Mata & von Helversen, 2015). With a view to communicative abilities preserved with age, language processing tasks might provide some insight into dynamic evolutive neurofunctional changes in healthy aging. However, it remains valuable to explore whether age-related neurofunctional changes can be detected during the aforementioned verbal fluency tasks, which exert self- initiated strategies.

Although numerous studies have explored the idea of age-related activation changes during language comprehension (Peelle, Chandrasekaran, Powers, Smith, & Grossman, 2013; Tyler et al., 2010; Wingfield & Grossman, 2006), a few have addressed neurofunctional reorganization issues in the domain of language production and, more specifically, word production comparing younger and healthy older adults (Chouiter et al., 2016; Marsolais et al., 2015; Meinzer et al., 2009). Overall, these studies have shown that bilateral frontal activations in older adults contribute to successful performance during comprehension tasks, but not always during production. The inconsistency posited by some neuroimaging findings illustrates the challenges associated with increased frontal activation as being the unique manner of improving verbal fluency performance in healthy aging.

In some neuroimaging studies using externally paced overt word production (Meinzer et al., 2012, 2009), additional right frontal involvement was reported as detrimental to performance maintenance for older adults, and was associated with decreased word production during semantic verbal fluency – unlike the phonemic fluency condition. Otherwise, Marsolais et al. (2015) found only marginal neurofunctional changes in high- performing older adults when they performed overt self-paced semantic and orthographic verbal fluency tasks. Although these authors suggested that neurofunctional changes during both verbal fluency tasks may be related to task demands, they found that a simple dissociation between semantic and phonemic/orthographic fluency are unlikely to describe all the underlying strategic components involved in verbal search processes. Also, it is worth noting that these strategic processes were found to be reduced or enhanced depending on whether the mode of production was controlled in covert mode or in overt-paced mode. The brain activations observed in silent mode were reported as more important than those involved in overt-paced word production (Basho et al., 2007; Birn, Cox, & Bandettini, 2004; Nagels et al., 2012). To the best of our knowledge, no neuroimaging study has yet explored neurofunctional changes underlying the strategic processes of verbal fluency tasks, and these as compared between healthy older and younger adults. Furthermore, this issue has not been thoroughly addressed in previous neuroimaging studies during overt self-paced verbal fluency tasks. The aim of this study was to describe age-related neurofunctional reorganization supporting strategic processes (clustering and switching) during both types of verbal fluency tasks (semantic and orthographic). To do so, an overt self-paced semantic and orthographic verbal fluency were performed within an innovative mixed functional magnetic resonance imaging (fMRI) design, which is used to mainly differentiate functional changes associated with clustering and switching strategies. Unlike previous neuroimaging studies on verbal fluency in aging, we used a relatively long period of time for word production (90s) to efficiently explore strategic components of spontaneous search so that performance could be more representative to typical behavioral context. Further, this methodological approach based on an innovative mixed block/event-related fMRI design (Donaldson, & Buckner, 2001; VissCher et al., 2003; Marsolais et al., 2015), allowed for valuable exploration of brain activity related to individual strategy productions (event-related activity), which could then also be grouped retrospectively in continuous blocks (block-related activity). The flexibility of a mixed block/event-related design was implemented so as to extract the evoked hemodynamic responses of strategic processes underlying fluency performance from block-related cerebral activations.

Two main results were expected in line with the study's aim:

- At the behavioral level, first, and based on the behavioral studies reported previously, verbal fluency based on semantic criteria would be performed by adopting more clustering strategy, and less switching, when comparing older adults to their younger counterparts. The second expected result was that older adults would show more switching between clusters, with smaller cluster size, than younger adults for the orthographic verbal fluency task.
- At neurofunctional level, and under such conditions, a larger activation of clusters in temporal regions, triggering clustering strategy, would be observed in older adults more so than in younger adults during semantic verbal fluency tasks. However, with consideration to the frontally mediated switching strategy, we expected in older adults that they would exhibit additional activation in the prefrontal regions when adopting switching strategy, so as to ultimately perform at the same level as the younger adults during orthographic verbal fluency tasks.

2. Materials and methods

2.1 Participants

Thirteen younger adults (range from 20 to 31, M = 24.23 years, SD = 3.91 years, 6 women) and 13 older adults (range from 60 to 73, M = 63.23 years, SD = 3.58 years, 7 women) were recruited from a pool of volunteers at the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM). All participants were right-handed (according to the Edinburgh Handedness Inventory; Oldfield, 1971) and native French speakers from Quebec (Canada). The two groups did not differ significantly in years of formal education ($M_{younger}$ = 16 years, SD = 1.68; M_{older} = 17.23 years, SD = 2.48) or gender distribution. Both groups had a normal or corrected-to-normal vision; none had a history of any major neurological disease, psychiatric illness, head injury, stroke, substance abuse or learning disabilities, or any difficulty that could interfere with the behavioral testing. Written informed consent was obtained from all participants according to the requirements of 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.

The two groups performed within the normal range on the Mini-Mental Status Examination (MMSE, M = 29.77, SD = 1.53; Folstein, Folstein, & McHugh, 1975). All participants were also submitted to a battery of neuropsychological tests that are tapping on the cognitive domains linked to the fMRI task, including inhibition, cognitive flexibility, and working memory using the Stroop Victoria Test (SVT; Regard, 1981), the Trail-Making Test (TMT, part A & B; Reitan, 1971), and the Alpha-span task test (Belleville, Rouleau, & Caza, 1998). The neuropsychological battery was administered during one session of approximately 60 min prior to the neuroimaging session. The descriptive data regarding socio-demographic and raw cognitive measures for younger and older groups are reported in Table 1.

In terms of raw cognitive performance, the older adults showed a significant decrease on speed of information processing, inhibition (while controlling for processing speed using a ratio score color-word – color)/color-word + color) and cognitive flexibility measures, compared to the younger adults. However, using standardized test scores to control for normal age-related differences, only cognitive flexibility (Trail Making test, Part B; $p < .01$) and working memory (immediate verbal serial recall, Alpha Span; $p < .01$) measures showed significant age-related decreases in performance (not shown in Table 1). For each group, a standardized executive functioning composite score (z-score) was also calculated by averaging the inhibition, the cognitive flexibility, and the working memory test scores. Based on this executive composite score, the older adults showed a significant decrease in their executive abilities compared to the younger adults. Nevertheless, all the participants had a cognitive functioning within the normal range according to the available normative data used for each neuropsychological test.

A power analysis suggested that a sample size of 13 participants per group should be sufficient for the verbal fluency task (e.g., 80% power at the .05 level of significance), thus the magnitude of the difference between younger and older adults reflects a large effect size. Moreover, a large number of verbal fluency studies have used relatively a same sample size (Gurd, 2002; Marsolais et al., 2015). In order to ensure the normality of data distribution and variance between the two groups, the test of Kolmogorov–Smirnov and test of Levene were conducted respectively. None of these tests had reached statistical significance.

2.2 Scoring method

The verbal fluency task involved four semantic criteria (animals, clothing, vegetables, and sports) and four orthographic criteria (P, M, L, and V) that were adapted from Cardebat, Doyon, Puel, Goulet, and Joanette (1990) and Goulet, Joanette, Sabourin, and Giroux (1997). For both semantic and orthographic fluency tasks, four measures were obtained for each participant: (1) the total of words produced, excluding perseverative errors and intrusions errors; (2) the cluster size; (3) the number of switches; and (4) the number of clusters. Cluster size: a “cluster” was defined by the number of words consecutively generated within the same orthographic (e.g., marchand, marque, marteau) or to the same semantic cluster (e.g., lion, elephant, tiger, giraffe). For clusters size, we counted from the second word in each cluster (e.g., a 4-word cluster counted as a cluster size of3). Also, for the number of switches (referred to as “switching” by Troyer et al. (1997), was calculated as the number of times a participant changed from one cluster to another, one cluster to a single word generated outside a cluster, and between single words. Thus, the number of switches may provide an indication regarding the strategic retrieval processes while cluster size reflects the extent of lexico-semantic knowledge (Robert et al., 1998; Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998). Moreover, the method for scoring in the present study was also based on Raskin’s study by including the number of clusters as more specific measure of transition between clustered words, without single words, in order to further explore the relative contribution of executive processes to produce related words (Elvevåg, Fisher, Gurd, & Goldberg, 2002; Hurks et al., 2010; Raskin et al., 1992). The scoring method included errors and repetitions in the clustering and the switching analysis because any word provides information to strategy underlying fluency performance (Ho et al., 2002; Koren, Kofman, & Berger, 2005; Zakzanis, McDonald, & Troyer, 2013). Detailed scoring of clustering and switching was conducted following the procedure developed by Troyer et al. (1997) and Troyer (2000). The semantic clusters’ sorting was determined a priori (e.g., animals), or was defined after analyzing the responses produced by all participants (e.g., clothing). Guidelines were created for scoring consistency between raters and the adaptation was made to predefined semantic sub- categories (clusters) based on the procedure developed by Gierski and Ergis (2004). An overview of semantic categories (animals, clothing, vegetables, and sports) and examples are provided in supplementary material. For orthographic fluency, clusters’ scoring was similar to Troyer et al. (1997) (for further details and scoring examples refer to their Appendix). However, to ensure the reliability of the clustering scoring, the guide- lines and clustering procedure were given to two raters, blind to the purpose of the study.

The Cohen's Kappa coefficients for inter-rater reliability obtained for the semantic fluency (Cohen's Kappa = .862, $p < .001$) and orthographic fluency (Cohen's Kappa coefficient = .927, $p < .001$) tasks were very high. This indicates that the procedure developed for calculating clusters size and switching was reliable.

T-tests were conducted on four components (number of words produced, cluster size, number of clusters, and number of switches) for each fluency tasks (semantic and orthographic) and four criteria of each fluency are combined. Additionally, the relationship between executive components of verbal fluency task and neuropsychological measures was examined by Pearson's correlations analysis. Statistical analyses were conducted using SPSS 18.0 for Mac.

2.3 MRI procedure

2.3.1 Data acquisition

Participants were scanned using the 3T Siemens Trio Magnetom MRI scanner at the Unité de Neuroimagerie Fonctionnelle (UNF) of the Centre de Recherche l'Institut Universitaire de Gériatrie de Montréal. The scanning session began with a high-resolution T1- weighted three-dimensional volume acquisitions for anatomical localization (voxel size, $1 \times 1 \times 1$ mm^3), followed by a single functional run of echoplanar T2*-weighted images with BOLD contrast acquisitions (TE, 30 ms; FA, 90°). Functional images were acquired every 2 s during 1600 s in a single run containing 800 volumes, and each volume contained 28 slices of 5 mm thick acquired in an inclined axial plane aligned to the anterior and posterior commissures with a matrix size of 64×64 pixels (voxel size, $3 \times 3 \times 5$ mm^3). Stimuli presentation and scanning were synchronized at the beginning of the run.

2.3.2 fMRI task design

This study was an original fMRI protocol followed a mixed-designed procedure using a self-paced overt verbal fluency task, which a block of trials occurred as participants were asked to generate as many words starting with the same letter or from the same semantic category. Likewise, this innovative mixed fMRI design will be reliable to explore a spontaneous and self-initiated driven strategy during verbal fluency task and to be therefore closely representative of typical behavioral word production. This methodological approach has been successfully tested within the previous study conducted by our laboratory members (Ansado, Marsolais, Methqal, Alary, & Joanette, 2013; Marsolais et al., 2015).

The fMRI session consisted of eight 90-s blocks of a control task and eight 90-s blocks of verbal fluency tasks (four semantic and four orthographic). At the beginning of the acquisition, the protocol started with a resting period, followed by the control condition, another resting period, and then a semantic or orthographic self-paced overt verbal fluency task. The order of presentation was counterbalanced among participants and the presentation of semantic and orthographic criteria alternated with the control condition. All blocks were preceded by a 10-s resting period within a single fMRI acquisition that lasted 26.39 min. The fixed length of 10-s for each resting period was chosen as a reasonable delay to allow adequate relaxation of the hemodynamic response between task blocks (Marsolais et al., 2015). During the rest period, a blank screen was presented and participants were instructed to keep looking at it, relax and avoid speaking. The verbal fluency tasks consisted of eight separate 90-s period wherein participants overtly generated as many words as possible that either started with the letter (producing words beginning with a given letter) or belonged to the category (producing words from a specific category) until the visual cue disappears. During the control condition, the word “MOIS [MONTH]” was presented in the middle of the screen for 90 s and participants continuously name aloud all the months of the year in chronological order until the cue disappeared. However, semantic and orthographic processing is minimized, as this task has proven to be “overlearnt” and with minor cognitive effort. In previous fMRI studies (Amunts et al., 2004; Gurd, 2002), the repetition of the months of the year was used as a control condition for verbal fluency tasks. The visual cues were presented in white font on a black background. All participants were also asked to avoid using proper nouns and repeating the same word within a condition.

Considering the aim of the study, a primary cognitive focus was based on the grouping specific strategic process of the word production and more specifically to the functional correlates associated with the generation of words from the same category (i.e., clustering) versus words from another category (i.e., switching). The strategic processes (clustering and switching) produced during the semantic and orthographic verbal fluency tasks were modeled as events (event-related verbal fluency) and grouped retrospectively in blocks to explore ongoing cognitive processes (Block-related activity) (Marsolais et al., 2015; Ollinger, Corbetta, & Shulman, 2001). The control task was defined as a block since the self-paced word generation rate in this condition was generally found to be too fast (e.g., 1 word every 1–2 s) to allow for meaningful event-related analyses.

A clustering period starts at the beginning of word production within the same subcategory and finishes with the production of the last word from the same sub- category. In a situation where a cluster could be categorized into two clustering strategies, the broader and the superordinate one was used to reflect an efficient semantic knowledge search network. For example, if an individual begins with a cluster of the fish category on semantic fluency (sole, trout, sardine), then produced a cluster of north of America animals (otter, marmot), this would be scored within the superordinate category of aquatic animals (e.g., Gierski & Ergis, 2004; Lanting, Haugrud, & Crossley, 2009, Troyer et al., 1997). A switching event is described as shifting to another subcategory, in other words, it consists the production of a single word from a different subcategory than the previous one. A switching event is defined as the period in which a word from a different subcategory is produced and the period of time considered that corresponds to the beginning and the end of the production of this particular word.

During the fMRI session, the verbal fluency tasks were presented on the computer using E-Prime software (Psychological Software Tool, 2002 retrieved from http://www. pstnet.com) and projected on a screen visible inside the scanner via a mirror attached on top of the head coil. The productions were recorded via an MRI compatible microphone (MR-Confon, GmbH, Germany) connected to a tape recorder (DAT) placed in the control room. Each participant's overt responses were subsequently transcribed while recording production time onset (in centiseconds) to ensure exact timing of prompts and to allow an event-related analysis within the task blocks. Both correct and incorrect productions during the verbal fluency tasks were considered for the behavioral and imaging analysis. Because the recordings contained high-volume scanner noise and unintelligibility of the vocal responses, Audacity program 1.3.12 beta software was used to decrease the volume of the scanner noise considerably after equalization, which contributed to improve the audibility of productions. Twenty-six audio files were obtained and transcribed into text files by three colleagues.

2.3.3 Data analysis

The fMRI data were analyzed using fMRIstat software developed by Worsley et al. (2002). For the analysis, the first three frames of the functional run were discarded. Functional images were first realigned to the fourth frame for motion correction and smoothed using a 6-mm full width half-maximum isotropic Gaussian kernel. Visual inspection of motion translation parameters revealed that, with the exception of one participant who showed two isolated spikes of random movement slightly greater than the fMRI voxel size of $3 \times 3 \times 5\text{mm}^3$, no other maximum values exceeded 3 mm in any direction and no obvious signs of motion-related artifacts were observed in the subsequent fMRI analysis. The statistical analysis of the fMRI data was based on a general 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 modeled as an autoregressive process. At each voxel, the autocorrelation parameter was estimated from the least squares residuals, after a bias correction for the 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 reestimated 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 nonlinear transformation into the standard proportional stereotaxic space of Talaraich and Tournoux (1988) using the MNI305 brain as an approximation via the algorithm of Collins, Neelin, Peters, and Evans (1994). Anatomical images were also normalized to the MNI space using the same transformation.

In a second step, subjects were combined using 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. Intergroup 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, 2005; Worsley et al., 2002). Movement parameters obtained during preprocessing were included as covariates of no interest to reduce the residual variance and the probability of movement-related artifacts. Statistical maps were set at a threshold ($p < .05$) correcting for multiple comparisons using the minimum between a Bonferroni correction and random field theory in the single and inter-group analysis. This yielded a threshold of t-statistic equal to or above 4.40 for a single voxel or a cluster size larger than 540 mm^3 for significance assessed on the special extent of the contiguous voxel (Friston et al., 1994). Significant peaks are reported using the minimum p-value of the single peak and cluster analysis. All peaks (minimum 10 mm cortical inter-peak distance and excluding cerebellar regions) that reached $p < .05$ corrected are reported. Peaks within the inferior temporal cortex and lateral prefrontal cortex that were observed in the literature using VFT in healthy adults (Birn et al., 2010; Meinzer et al., 2012; Troyer et al., 1997) were considered predicted and are reported at a significance of $p < .001$ uncorrected. We indicated by an asterisk (*) in the tables. Four contrasts were generated for the comparison between conditions, while one statistical map was produced for the correlation analysis. We examined the following contrasts: (1) semantic clustering minus control condition; (2) semantic switching minus control condition; (3) orthographic clustering minus control condition; and (4) orthographic switching minus control condition. Additionally, we performed a correlation analysis on the semantic fluency task, for younger and older adults. To do that, we assessed the effect of the ordering of word production within a cluster on the BOLD signal while performing all active conditions. In this analysis, the order was added as a covariance of interest for each condition not contrasted.

3. Results

3.1 Behavioral results

3.1.1 Age-related differences in clustering and switching processes

In terms of the total of correct words produced, the older adults performed as well as the younger adults, irrespective of the nature of the verbal fluency task: semantic ($M_{older} = 79.76$, SD = 17.54; $M_{younger} = 88.30$, SD = 16.66, $p = .57$) and orthographic ($M_{older} = 83.61$, SD = 25.30; $M_{younger} = 82.15$, SD = 23.09, $p = .42$). In terms of the number of errors made during semantic and orthographic fluency tasks, a difference between younger and older adults did not reach statistical significance ($M_{older\_semantic} = 4.46$, SD = 7.77; $M_{younger\_semantic} = 1.76$, SD = 1.83, $p = .23$; $M_{older\_orthographic} = 2.53$, SD = 2.56; $M_{younger\_orthographic} = 0.77$, SD = 1.01, $p = .11$). As for strategic processes, the older adults produced significantly larger clusters size than the younger adults, while they made globally a smaller number of clusters and fewer switches than the younger adults for semantic fluency task.

However, the older adults carried out as many larger clusters and many numbers of switches and clusters as the younger adults for orthographic fluency task, but the differences were not statistically significant (Table 2).

3.1.2 Relationship between cognitive measures and strategic processes

Since the cognitive abilities potentially underlie strategic processes in two verbal fluency tasks (semantic and orthographic), Pearson correlation analysis was performed to explore the relationship between cluster size, number of clusters and number of switches and the executive ability indexes for younger and older adults respectively. For semantic verbal fluency, the number of words produced was positively correlated with the number of clusters [$r(26)_{younger} = .91$; $p < .001$; $r(26)_{older} = .81$; $p < .001$] and number of switches [r(26)younger = .52; $p < .05$; $r(26)_{older} = .52$; $p < .05$] for two groups, such that more clusters were associated with better semantic performance. Cluster size was related to performance for the older group only [$r(26)_{younger} = .28$, $p = .17$; $r(26)_{older} = .46$, $p = .05$]. For orthographic verbal fluency, the number of words produced was positively correlated with the number of clusters [$r(26)_{younger} = .93$, $p < .001$; $r(26)_{older} = .88$, $p < .001$] and number of switches [$r(26)_{younger} = .81$, $p < .001$; $r(26)_{older} = .74$, $p < .01$] for two groups. Cluster size was related to performance on orthographic verbal fluency only for the younger adults [r(26) younger = .73, $p < .01$; $r(26)_{older} = .-12$, $p = .34$]. However, number of switches was positively correlated with the number of clusters for younger [$r(26)_{younger} = .78$, $p < .001$] and negatively with cluster size for older adults [$r(26)_{older} = -.58$, $p < .01$]. A correlation analysis performed between the executive ability indexes and strategic components revealed significant negative correlation between executive ability indexes and orthographic cluster size [$r(26) = .-56$, $p < .05$] for older adults only. No other significant correlation was found between executive composite score and strategic processes.

3.2 fMRI results

3.2.1 Semantic clustering versus control condition

When semantic clustering was compared with control condition (Table 3 and Figure 1), the younger adults showed significant activations in the left ventrolateral prefrontal cortex (BA 45), the left dorsolateral prefrontal cortex (BA 9/46), the anterior cingulate bilaterally (BA 32), the supplementary motor area, SMA bilaterally (BAs 6 and 8), the left lateral posterior prefrontal cortex (BA 8), the left lateral premotor cortex (BA 6), the left posterior inferior parietal cortex (BA 40), and the right superior temporal cortex (BA 22). There was also significant bilateral subcortical activation in the caudate nucleus, the putamen, the thalamus, and also in the cerebellum cortex. The older adults showed significant activation in the SMA (BAs 6 and 8), the lateral posterior prefrontal cortex (BA 8) bilaterally, the left inferior frontal cortex (junction 6/8/44), the right middle temporal cortex (BA 21), the bilateral inferior temporal cortex (BA 37, fusiform area), and the left occipital cortex (BA 17). The intergroup comparison groups showed significant activations in the right inferior temporal cortex (BA 37) for older adults when compared to younger adults. However, the reverse comparison showed significant activation in the right cingulate cortex (BA 23) and in the left inferior temporal cortex (BA 38) for the younger adults.

When we performed a correlation analysis to explore the evolution of the BOLD signal within semantic clustering, significant positive correlation was observed in the left lateral posterior prefrontal cortex (BA 8) and the inferior temporal cortex (BA 37) as well as the left cerebellum for the older adults whereas the younger adults showed significant activation in the left lateral posterior prefrontal cortex (BA 8), the SMA (BAs 6 and 8), the left inferior prefrontal cortex (Junction 6/8/44), the anterior cingulate cortex bilaterally (BA 32), as well as subcortically, in the left putamen and the left caudate nucleus and the cerebellum bilaterally (Table 4 and Figure 2).

3.2.2 Semantic switching versus control condition

When semantic switching was compared with control condition (Table 5), the younger adults showed significant activation in the left ventrolateral prefrontal cortex (BA 44/45), the dorsolateral prefrontal cortex (BA 9/46) and the left SMA (BAs 6 and 8). The older adults showed significant activation in the left SMA (BAs 6 and 8) and in the left inferior temporal cortex (BA 37, fusiform area). The intergroup comparison showed significant activation in the right caudate nucleus for the younger adults when compared to the older adults. However, the reverse comparison showed significant activation in the left middle temporal cortex (BA 20) for the older adults.

3.2.3 Orthographic clustering versus control condition

When orthographic clustering was compared with the control condition (Table 6), the younger adults showed significant activation in the left ventrolateral prefrontal cortex (BA 44/45), the anterior cingulate cortex (BA 32), the left posterior prefrontal cortex (junction 6/8/44), the left SMA (BAs 6 and 8), the posterior inferior parietal cortex (BA 40), and the left caudate nucleus. The older adults showed significant activation in the left ventrolateral prefrontal cortex (BA 47/12), the left inferior frontal cortex (Junction 6/8/44), the SMA bilaterally (BAs 6 and 8), the left inferior parietal cortex (BA 40), and the left inferior temporal cortex (BA 37, fusiform area). The intergroup comparison showed significant activation in the right middle temporal cortex (BA 21) and the left inferior temporal cortex (BA 37) for the younger adults when compared to the older adults. However, no significant activation difference was observed for the reverse comparison when the older adults were compared to the younger adults.

3.2.4 Orthographic switching versus control condition

When orthographic switching was compared with the control condition (Table 7 and Figure 3), the younger adults show significant activation in the left ventrolateral prefrontal cortex (BAs 44/45 and 47/12), the dorsolateral prefrontal cortex (BA 9/46), the left posterior prefrontal cortex (BA 44), the anterior cingulate cortex bilaterally (BA 32), the left SMA (BAs 6 and 8), the left lateral posterior prefrontal cortex (BA 8), the left middle temporal cortex (BA 21), as well as subcortically in the left caudate nucleus and the left thalamus. However, the older adults showed significant activation in the left posterior prefrontal cortex (junction 6/8/44), the SMA bilaterally (BAs 6 and 8), the left lateral premotor cortex (BA 6), and the left inferior temporal cortex (BA 20). The intergroup comparison showed significant activation in the left anterior cingulate (BA 32) for the younger adults when compared to the older adults. However, significant activation difference was observed for the reverse comparison in the right posterior prefrontal cortex (BA 6/8) when the older adults were compared to the younger adults.

4. Discussion

The goal of this study was to explore the age-related neurofunctional reorganization that underlies clustering and switching strategies in semantic and orthographic fluency tasks for high-performing healthy younger and older adults. To achieve this purpose, an overt self-paced fluency task was performed within an original mixed fMRI design (Marsolais et al., 2015). Our results suggest that the preservation of verbal fluency performance in healthy aging was associated to significant brain activation changes through distinct cognitive strategic processes. Our main findings showed two characteristics. First, older adults engaged bilateral inferior temporal regions to a greater extent than their younger counterparts during usage of semantic clustering strategy, probably reflecting an enhanced expert use of acquired knowledge and efficient organization of inner lexicon. Moreover, a positive correlation was found between activations in temporal region and the progression of word production within the semantic cluster for both adult groups. Second, unlike younger adults, older adults had recruited bilateral frontal regions during orthographic-switching strategy to support high executive process demands.

At the behavioral level, although the total number of words correctly produced was similar between the younger and the older adults, either age group used different strategic processes during the semantic and the orthographic verbal fluency tasks. As expected, the two strategic processes were related to fluency performance (total words produced) for both groups, though high-performing older adults used clustering strategy to an advantage during the semantic fluency task. Likewise, our correlation analyses indicated that a total number of words produced during the semantic fluency tasks was more correlated with the number of clusters than the number of switches. These findings are coherent with previous studies reporting the relevance of switching between clusters of associative words or single words for optimal performance in the two age groups (Hughes & Bryan, 2002; Troyer et al., 1997). However, significantly larger semantic clusters were found in the older adults group, compared to their younger counterparts, which may reflect their ability to take advantage of semantic knowledge to a greater extent than the younger adults. Thus, as long as self-initiated and internally guided strategies were invoked during word production, the older adults found a better way to manage their limited resources with a less costly cognitive strategy, as opposed to one of switching, which places excessively high demands on executive resources. This interpretation could be considered in light of the evidence provided by Hedden and Gabrieli (2004). These authors observed in older adults that an improvement of verbal knowledge and expertise through life promotes efficient word production through unique strategies that are not available in younger adults. According to these observations, the behavioral pattern of semantic-clustering strategy observed in highly educated older adults suggests that the adoption of distinctive cognitive strategies leads to high performance maintenance, at a similar level as the younger adults. Along these lines, some studies have reported that greater fluency performance in older adults, relative to younger ones, might have been related to a higher level of education with the use of broader vocabulary, also under- pinned by efficient strategies (e.g., Bolla, Lindgren, Bonaccorsy, & Bleecker, 1990; Kahlaoui et al., 2012; Tombaugh, 1999). Other evidence, resulting from the cognitive reserve concept (Stern, 2002, 2009), suggests contribution from verbal proxies, owing to years of formal education undergone by subject, leading to efficient network selection that could take advantage of a large repertoire of strategies in healthy aging. Similarly, Barulli and Stern (2013) have reported that a higher cognitive reserve based on a high verbal intelligence quotient and years of education in healthy older adults, reflects an ability to better select efficient strategies in successfully performing verbal tasks. On the basis of evidence showing knowledge-driven expertise through a life span, changing processing strategies could be associated with evolutive and unique neurofunctional resources during healthy aging (Aine et al., 2006; Cabeza, 2002; Greenwood, 2007; Greenwood & Parasuraman, 2010).

At a neurofunctional level, neuroimaging findings in our study revealed significant age-related activations during semantic clustering in inferior temporal regions, bilaterally for older adults as opposed to unilateral activation in the younger adult group (Figure 1). As expected, this age-related change in hemispheric lateralization may reflect neural support for proper cognitive strategies that can be assumed to have beneficial effect on semantic fluency performance. Therefore, these patterns of activation suggest that strategy change, at least for the high-performing older adults, does not consistently make youth-like brain activation, but is rather able to maintain performance through distinct cognitive strategies and shift neural activation to requisite brain regions. In the same vein, previous studies have shown additional temporal recruitment in older adults during semantic categorization tasks, for which their younger counterparts are left-lateralized, despite an equivalent performance at the behavioral level (Lacombe, Jolicoeur, Grimault, Pineault, & Joubert, 2015; Martins, Simard, & Monchi, 2014). Moreover, the right hemisphere involvement has also been proven to be relevant, in studies of brain-damaged subjects, in maximizing exploitation of semantic subfields for semantic fluency (Joanette, Goulet, & Hannequin, 1990). This view is consistent with data suggesting that the right temporal cortex maintains diffuse activation of a broader semantic field while the homologous left cortex still supports a strong categorical semantic activation (Jung-Beeman, 2005; Zhang et al., 2016). In accordance with this evidence, Thompson, Henshall, and Jefferies (2016) have also reported a role of the right temporal cortex in controlling retrieval during an access of knowledge from the semantic store. Taken together, this evidence may support a potential contribution of the contralateral activations as semantic cognitive strategy neural support.

Against this view, one fMRI study using an overt semantic fluency task (Nagels et al., 2012) has reported a negative correlation between the additional temporal activation and word knowledge in older adults. Nevertheless, it is worth noting that a short production period (12s) used in this latter study was probably insufficient to capture beneficial role of additional temporal recruitment. This assumption has been addressed in some behavioral studies (Raboutet et al., 2010; Sauzéon et al., 2011) where the more extensive an older adult's verbal knowledge, the more enhanced their performance as observed later in the time delay. Therefore, given the left lateralization of semantic processing, the right hemisphere contribution seems to be linked to the most active or effortful last period of word production when compared to a more automatic one, which activates lexico-semantic store and requires less controlled memory search (Joanette et al., 1990).

In this regard, to further explore the age-related neurofunctional changes reported in the current study, the following correlation analysis was made between brain activation changes and the progression of word production within the semantic cluster for both adult groups. A significant activation during word production of semantic clusters in the left inferior temporal cortex (BA 37) was found for the older adults, while the left inferior prefrontal cortex (junction 6/8/44) and the left subcortical regions (left putamen and left caudate nucleus) were more relevant for the younger adults (Figure 2). The involvement of fronto-subcortical regions is consistent with other studies that have reported activation in the caudate nucleus during semantic categorization (Ansado et al., 2013; Simard, Monetta, Nagano-Saito, & Monchi, 2013) and during word production in younger adults (Crosson et al., 2003).

Of note is the observed link between posterior activations and successful semantic fluency performance, which is consistent with some studies that support the idea of the involvement of temporal regions as sustaining semantic integration, while frontal regions are crucial for controlled semantic retrieval (Lacombe et al., 2015; Wagner, Paré-Blagoev, Clark, & Poldrack, 2001). Thus, semantic fluency performance in older adults might reflect a dynamic reallocation of neural resources within the semantic pathway (from caudate-nucleus to fusiform area), this being different to what is observed for younger adults performing the same task. These results highlight the existence of unique neurofunctional patterns as another mechanistic explanation of age-related maintenance of cognitive abilities in healthy high-performing older adults. The efficiency of semantic verbal fluency appears to be not exclusively restricted to frontal regions but is mainly dependent on temporal regions, triggering mainly the exploitation of semantic lexical storage in the high-performing older adults; meanwhile the younger participants appear to rely more on exploration (or switching) strategies, as there is more unilateral activation of fronto-subcortical regions.

Similarly, in an fMRI study, Simard et al. (2011) have proposed that matching according to the same semantic rules during a Wisconsin Word Sorting Test required caudate nucleus activation for younger adults as a functional manifestation of the ability to enhance suppression of competing categories among other choices in order to perform a task. In other words, in the younger group, the fronto-striatal regions seem to be more implicated than temporal regions during semantic processing tasks.

More recently, Kennedy et al. (2015) have reported some striking findings: first, despite age invariability in canonical semantic network activation, a cerebral asymmetry reduction with age was more evident in the inferior temporal regions, corroborating the notion of verbal knowledge preservation in healthy aging. Secondly, the age-related activation shift into posterior brain regions has likely been driven by hitting a neural resource ceiling in the latest developed brain structures (i.e., frontal regions). Accordingly, the authors concluded that changes in neural activation throughout a life span play a role in determining successful performance in lexico-semantic tasks. Moreover, in context of dopamine depletion in fronto-striatal circuitry (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006), the age-related activation shift in the temporal regions could act as form of scaffolding (Reuter-Lorenz, 2002) to improve behavioral performance. This interpretation seems to be coherent with the STAC model, providing some evidence of neural scaffolds in support for effective strategy selection, as well as in reliance on specific brain regions in response to task-related challenges and limited resources (Barulli & Stern, 2013; Lövdén et al., 2010; Reuter-Lorenz & Cappell, 2008). Consequently, the activation changes in healthy high-performing older adults appear to be compatible with the idea that contribution of semantic pathway streams in semantic verbal fluency triggers unique neurofunctional reorganization, which is necessary to maintain performance at a higher level. It follows that brain activation differences between older adults and their younger counterparts are in agreement with the presumed neurofunctional reorganization resources for semantic processing (Lacombe et al., 2015; Diaz, Rizio, & Zhuang, 2016). Taken together, performance maintenance in healthy aging appears to depend on the strategy change (i.e., clustering) in concomitance with the involvement of inferior temporal regions (fusiform area) instead of frontal regions as in the younger counterparts reflecting a different way to perform the same task. Overall, this dynamic neural reallocation reflects the ability to mobilize knowledge-based strategy (i.e., semantic clustering) to improve performance in healthy high-performing older adults. Hence, in the context of age-related equivalent total words produced, but with differential strategy use (more clustering than switching), the changes in neural activity within semantic neural networks suggest that specific brain regions, such as the inferior temporal cortex, could provide a form of neural scaffolding for high-performing healthy older adults, in order to cope with decreased prefrontal and caudate activity.

Consistent with these notions, Craik and Bialystok (2006) proposed that cognitive aging could be understood in terms of expertise based on an interaction of factors such as maturation, learning experience, and processing efficiency differences throughout the life span. Furthermore, the cognitive changes that influence performance brings dynamic neurofunctional patterns and appropriate processing strategies with aging (Greenwood, 2007). Thus, for older adults, a switching strategy might represent a more effortful and less beneficial strategy than clustering in successfully performing a semantic fluency task.

The present study has also revealed significant activation in the left middle temporal region (BA 20) for the older adults compared to the right caudate nucleus for the younger adults during switching strategy in the semantic verbal fluency task. These results reveal that high-performing older adults seem to rely on the semantic pathway (middle temporal cortex BA 20), which is consistently recruited by executively demanding semantic processes (Noonan, Jefferies, Visser, & Ralph, 2013; Whitney, Grossman, & Kircher, 2009). However, the involvement of caudate nucleus by younger adults appears to rely on the execution of a self-generated set shift for this group (Monchi, Petrides, Strafella, Worsley, & Doyon, 2006). As stated by Simard et al. (2011), the processes required to plan switching to new rule retrieval are also required when choosing among different semantic categories. Indeed, switching could reflect the ability to disengage from a previous strategy or may be related to the ability to initiate a new strategy. Also, Mayr and Kliegl (2000) have argued that executive processes sustain each act of retrieval, while switching between semantic clusters is genuinely semantic-based processing. These authors suggest that if verbal abilities are more preserved over time than executive functioning, then changes in strategy for verbal tasks can take advantage from a broader lexical storage. However, the precise nature of switching strategy in verbal fluency is still not clear for the older adults, with regard to an underlying cognitive process.

It should be noted that the age-related cognitive changes are probably not triggered by decrease in executive functioning, but instead the impact of executive abilities on managing trade-offs between exploration and exploitation strategies as the subjects attempt to reach task demands

(Hills,Todd, & Goldstone, 2008, 2010). In this regard, a switching strategy in semantic fluency seems to be a less worthwhile effort for older adults. Already reported by several authors (Abwender, Swan, Boweman, & Connolly, 2001; Mayr, 2002) is the challenge posed by age-differences, in semantic fluency, to the stated view relative to orthographic performance suggesting no age effect, albeit executive-dependent processes do place high demands on resources during orthographic fluency tasks. Consistent with older adults' limited resources account, a total amount of available processing resources do not drop with age, but are affected by the efficiency of neural resources engaged (Craik & Bialystok, 2006). From a cognitive aging standpoint, some studies have even suggested that there is no age-related executive decline (Boone, Miller, Lesser, Hill, & D'Elia, 1990) and successful aging has been related to flexible and optimal use of its resources (Kramer, Hahn, & Gopher, 1999; Adrover-Roig et al., 2012). However, we believe that more studies are needed to clarify our understanding of the age-related executive switching processes in semantic and orthographic fluency tasks.

As stated in the introduction, we can also assume that trade-offs between exploitation (clustering) and exploration strategies in search processes depend on the task requirements, since older adults invoke more exploration strategy in orthographic production context and show more advantage in stopping exploitation and initiate exploration to succeed a task (Hills et al., 2010). A performance difference between older and younger adults, found in the present study, has been indexed by temporally mediated clustering strategy used for performing the semantic verbal fluency task. In contrast, the orthographic fluency task is thought to be dependent on more frontally mediated switching strategy due to demanding control search processes such as cognitive flexibility and working memory (Hughes & Bryan, 2002; Muller, Mérillat, & Jäncke, 2016). This ability to recall a word starting with the orthographic criteria is associated with more effortful switches between clusters that should predict increases in behavioral performance (Elvevåg et al., 2002; Hoyau, Cousin, Jaillard, & Baciu, 2016; Koren et al., 2005).

This view is compatible with our behavioral findings from the orthographic fluency task. A similar level of performance was found between the older and the younger adults in terms of total words produced and the tendency for clustering and switching in order to maintain a good level of performance. Interestingly, the cluster size in orthographic fluency was associated with total word production performance for both groups but negatively so for the older adults. Moreover, a correlation between the cluster size and the number of switches did not follow the same trend for the older adults (negative) and the younger adults (positive). This pattern of results possibly reflects a production of smaller cluster size by older adults faced with orthographic criteria due to effortful search processes of words beginning with a specific letter. Further, this assumption is consistent with findings reported by Hughes and Bryan (2002) on what allows maintenance performance in healthy high-performing older adults. These authors reported a production of small clusters in the older group such that fewer words per cluster were related to better performance in orthographic fluency. This may be due to the fact that the older group produced smaller clusters of words and switched more between them than did the younger group, but the difference was not statistically significant. From a cognitive perspective, it is apparent that cognitive processes are common to both fluency tasks (attention, initiation strategies, inhibition processing to avoid perseveration and intrusion, and working memory), but at different degrees of association with aging. In addition, the cognitive processes supporting orthographic fluency appear to be relying on executive index for older adults (working memory, cognitive flexibility and inhibition). To this end, a correlation analysis was used to assess associations between strategic processes and executive measure for both adults group. These correlations revealed a negative relationship between cluster size and executive composite measure only for older adults. This may indicate that the number of clusters and number of switches on orthographic verbal fluency were both related to optimal performance in both groups but in different manner. The older group's performance in the orthographic fluency task is consistent with previous studies which emphasized a mediation of knowledge-based strategy (i.e., clustering) as useful support of language production abilities into higher ages (Sauzéon et al., 2011). Importantly, the executive functioning appears to be associated more with orthographic performance in the older group than in the younger one.

Behind the maintenance of a good orthographic fluency performance in older and younger adults, significant patterns of functional neuroimaging findings reveal frontal activation changes, mainly in older adults, to shrink a gap between behavioral and functional patterns, since frontally mediated switching strategy is highly demanding in executive resources (Figure 3). These neurofunctional manifestations in frontal regions have been also explained by the HAROLD phenomenon and interpreted as neural expressions engaged by high-performing older adults to reach a high level of performance that leads to task success. Consistent with a sizeable number of neuroimaging studies, a bilateral frontal activation pattern observed in older adults may reflect increased cognitive demands in various tasks, such as episodic memory retrieval, inhibition control, or visual judgment. Our findings suggest that switching strategy process used during the orthographic fluency task may have been more challenged in our high-performing older group due to reduction in left frontal functioning in healthy aging (Baldo, Schwartz, Wilkins, & Dronkers, 2006; Hirshorn & Thompson-Schill, 2006; Meinzer et al., 2009; Troyer et al., 1997). In healthy aging, the ability to manage the interplay between verbal knowledge and executive abilities appear potentially depending on trade-offs between exploration and exploitation strategies to successfully perform the verbal fluency tasks.

It would be interesting to explore in further neuroimaging studies whether the type of strategy use varies with the level of production difficulty for both verbal fluency tasks comparing older and younger adults. For instance, whether differences in degree of reliance on strategic processes could be found inside semantic subcategories and at further extent whether differences in brain activation could be observed between younger and healthy older adults under such conditions.

The present study has some limitations that need to be addressed. Beyond the fact that the main purpose of the study was to explore functional and behavioral changes in verbal fluency performed primarily by cognitively healthy older adults, the extent of the subjective cognitive complaints (SCCs) was not carefully assessed among our older adult participants. Even though the relationship between the presence of complaints in elderly people and objective cognitive impairment (Sun et al., 2015) remains controversial, the future aging studies should consider, at the furthest extent possible, a close follow-up of older subjects with SCCs because of their increased risk for the conversion to Mild Cognitive Impairment, purportedly a marker of the transition from normal aging to Alzheimer's disease (AD) (Jensen et al., 2014; Markova et al., 2017). The age-related subjective complaints cannot reasonably be harbingers of early stages of dementia until we have longitudinal data to provide more evidence of the relationship between SCCs and decrement in fluency performance.

As another limitation in the present study, the age-related strategy differences inside different semantic categories (natural vs. artifacts) need to be addressed in future neuroimaging studies comparing older adults with and without cognitive complaints. Interestingly, in a recent behavioral study, Nikolai et al. (2017) suggest that age-related impairment in semantic verbal fluency is a potential predictor of subtle changes in patients with subjective cognitive decline (SCD). Unlike orthographic verbal fluency, and in terms of strategic components, the semantic verbal fluency impairment is detectable in very early SCD stage. Likewise, data suggest that patients with SCD are unable to use clustering and switching strategies in the same way as normal older controls during word production in more difficult categories, such as vegetables compared to animals. Specifically, the vegetables category has smaller size and number of clusters, leading to more difficulty with infrequent word recall from semantic memory.

On the other hand, a relation between posterior cortical regions (temporal cortex, hippocampus) and the differential of decreased performance of semantic categories fluency has been considered as a potential predictor of cognitive decline progression (Price et al., 2012; Glikmann-Johnston et al., 2015).

Also, given the complex impact of psychological factors (depression, anxiety, neuroticism) on the etiology of SCCs, the complaints may provide the opportunity to explore the progression of different pathological processes in AD (Cheng, Chen, & Chiu, 2017) Further longitudinal studies are needed to support both specificity and sensitivity of impact from these high-risk factors on the predictors of subtle loss in semantic knowledge in early preclinical stages beyond normal aging.

5. Conclusion

The present study is coherent with the literature, suggesting that patterns of brain activation sustaining equivalent performance during healthy aging could be under-pinned by different strategies as the brain changes. Our main findings indicate that temporally mediated semantic clustering and frontally mediated orthographic switching were driven by evolutive neurofunctional reorganization in high-performing older adults. Moreover, these differences in brain activation for changing tasks and strategic processes underlie the healthy older brain's capacity to maintain language production ability. In this way, a dynamic reallocation of neural resources may reasonably reflect the expression of other neurofunctional adaptations beyond the frontal regions in order to optimally use resources to maintain language performance. That being said, the expertise and knowledge-driven abilities revolve around the notion that knowledge (i.e., verbal abilities) acquired through a life span can be well maintained and account for the cognitive changes that occur in healthy aging (Bäckman & Dixon, 1992). By a confluent perspective, healthy aging represents an adaptive process requiring selective optimization between decline on one hand, and preservation of abilities on the other (Baltes & Baltes, 1990). Thus, a better performance does not mean acting youth-like in healthy aging but be able to adopt strategies based on task requirements. The ability to manage trade-offs between clustering and switching can be viewed as support of cognitive and neural resources evolution in healthy aging. Given the fact that age- related differences in semantic fluency performance are mainly explained by the extent of the clustering strategy use, it is, therefore, possible that could be viewed as being the option chosen under the selection pressure of healthy aging rather than compensatory strategy. Another explanation is that more reliance on switching strategy only occurs under orthographic condition since it is highly executive-dependent. As stated by Mata & von Helversen (2015), the verbal fluency performance profile in healthy aging appears to be based on picking an option where the gain is uncertain, but where there is an advantage of accumulating knowledge by following the appropriate strategy – as long as resources continue to be found. This assumption is consistent with the positive correlation found between executive composite index and switching strategy in only older adults group. In light of the STAC model (Park & Reuter-Lorenz, 2009), the neural scaffolds built up through life experiences and acquired knowledge might be critical to shrink a gap between behavioral and functional patterns to better maintain lexico-production ability in healthy high-performing older adults, as well as adopting appropriate and advantageous strategies to support the fulfillment of task demands.

To summarize, both behavioral and neuroimaging findings in the current study seem to suggest that the lifelong acquired expertise guides and supports the adoption of distinctive strategies through differential engagement of brain regions when it comes to verbal fluency tasks (semantic vs. orthographic) and cognitive processes (clustering vs. switching). To the best of our knowledge, the present study is the first that uses overt and self-paced verbal fluency tasks within an innovative mixed fMRI design comparing younger and healthy older adults. This methodological approach appears to be fully reliable for exploring the strategic components of word production as it emerges in the clinical context.

References

Abwender, D. A., Swan, J. G., Bowerman, J. T., & Connolly, S. W. (2001). Qualitative analysis of verbal

fluency output: Review and comparison of several scoring methods. Assessment, 8(3), 323–338.

Ackerman, P. L. (2008). Knowledge and cognitive aging. In: F. I. M. Craik & T. A. Salthouse (Eds.), The handbook of aging and cognition (3rd ed., pp. 445–490). New York: Psychology Press.

Adrover-Roig, D., Sesé, A., Barceló, F., & Palmer, A. (2012). a latent variable approach to executive control in healthy ageing. brain and cognition, 78(3),284–299. doi10.1016/j.bandc.2012.01.005

Adrover-Roig, D., Sesé, A., Barceló, F., & Palmer, A. (2012). A latent variable approach to executive control in healthy ageing. Brain and Cognition, 78(3), 284–299.

Aine, C. J., Woodruff, C. C., Knoefel, J. E., Adair, J. C., Hudson, D., Qualls, C., . . . Stephen, J. M. (2006).

Aging: Compensation or maturation? NeuroImage, 32(4), 1891–1904.

Amunts, K., Weiss, P. H., Mohlberg, H., Pieperhoff, P., Eickhoff, S., Gurd, J. M., . . . Zilles, K. (2004). Analysis of neural mechanisms underlying verbal fluency in cytoarchitectonically defined stereotaxic space—The roles of Brodmann areas 44 and 45. NeuroImage, 22(1), 42–56.

Ansado, J., Marsolais, Y., Methqal, I., Alary, F., & Joanette, Y. (2013). The adaptive aging brain: Evidence from the preservation of communication abilities with age. European Journal of Neuroscience, 37(12), 1887–1895.

Ansado, J., Monchi, O., Ennabil, N., Faure, S., & Joanette, Y. (2012). Load-dependent posterior-anterior shift in aging in complex visual selective attention situations. Brain Research, 1454(2009), 14–22. Bäckman, L., & Dixon, R. A. (1992). Psychological compensation: A theoretical framework. Psychological Bulletin, 112(2), 259–283.

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.-C., & Farde, L. (2006). The correlative triad among aging, dopamine, and cognition: Current status and future prospects. Neuroscience & Biobehavioral Reviews, 30(6), 791–807.

Baldo, J. V., Schwartz, S., Wilkins, D., & Dronkers, N. F. (2006). Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. Journal of the International Neuropsychological Society, 12(6), 896–900.

Baltes, P. B., & Baltes, M. M. (1990). Psychological perspectives on successful aging: The model of selective optimization with compensation. In: P. B. Baltes & M. M. Baltes (Eds.), Successful aging: Perspectives from the behavioral sciences (pp. 1–34). New York: Cambridge University Press.

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: Emerging

concepts in cognitive reserve. Trends in Cognitive Sciences, 17(10), 502–509.

Basho, S, Palmer, E. D, Rubio, M. A, Wulfeck, B, & Müller, R-A. (2007). Effects of generation mode in fmri adaptations of semantic fluency: paced production and overt speech. Neuropsychologia, 45 (8), 1697–1706. doi:10.1016/j.neuropsychologia.2007.01.007

Belleville, S., Rouleau, N., & Caza, N. (1998). Effect of normal aging on the manipulation of information in working memory. Memory and Cognition, 26(3), 572–583.

Birn, R. M., Cox, R. W., & Bandettini, P. A. (2004). experimental designs and processing strategies for fmri studies involving overt verbal responses. neuroimage, 23(3),1046–1058. doi:10.1016/j. neuroimage.2004.07.039

Birn, R. M., Kenworthy, L., Case, L., Caravella, R., Jones, T. B., Bandettini, P. A., & Martin, A. (2010). Neural systems supporting lexical search guided by letter and semantic category cues: A self- paced overt response fMRI study of verbal fluency. NeuroImage, 49(1), 1099–1107.

Bolla, K. I., Lindgren, K. N., Bonaccorsy, C., & Bleecker, M. L. (1990). Predictors of verbal fluency (FAS) in the healthy elderly. Journal of Clinical Psychology, 46(5), 623–628.

Boone, K. B., Miller, B. L., Lesser, I. M., Hill, E., & D'Elia, L. (1990). Performance on frontal lobe tests in healthy, older individuals. Developmental Neuropsychology, 6(3), 215–223.

Bryan, J., Luszcz, M. A., & Crawford, J. R. (1997). Verbal knowledge and speed of information processing as mediators of age differences in verbal fluency performance among older adults. Psychology and Aging, 12(3), 473–478. doi:10.1037/0882-7974.12.3.473

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: The HAROLD model. Psychology and Aging, 17(1), 85–100.

Cardebat, D., Doyon, B., Puel, M., Goulet, P., & Joanette, Y. (1990). Formal and semantic lexical evocation in normal subjects. Performance and dynamics of production as a function of sex, age and educational level. Acta Neurologica Belgica, 90(4), 207–217.

Cheng, Y. W., Chen, T. F., & Chiu, M. J. (2017). From mild cognitive impairment to subjective cognitive decline: conceptual and methodological evolution. Neuropsychiatric Disease and Treatment, Volume 13, 491–498. doi:10.2147/NDT.S123428

Chouiter, L., Holmberg, J., Manuel, A. L., Colombo, F., Clarke, S., Annoni, J.-M., & Spierer, L. (2016). Partly segregated cortico-subcortical pathways support phonologic and semantic verbal flu- ency: A lesion study. Neuroscience, 329, 275–283.

Collins, D. L., Neelin, P., Peters, T. M., & Evans, A. C. (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. Journal of Computer Assisted Tomography, 18(2), 192–205.

Craik, F. I. M., & Bialystok, E. (2006). Cognition through the lifespan: Mechanisms of change. Trends in Cognitive Sciences, 10(3), 131–138. doi:10.1016/j.tics.2006.01.007

Craik, F. I. M., & Byrd, M. (1982). Aging and cognitive deficits. In Aging and Cognitive Processes (pp.191–211). Boston, MA: Springer US. doi:10.1007/978-1-4684-4178-9_11

Crosson, B., Benefield, H., Cato, M. A., Sadek, J. R., Moore, A. B., Wierenga, C. E., … Briggs, R. W. (2003). Left and right basal ganglia and frontal activity during language generation: Contributions to lexical, semantic, and phonological processes. Journal of the International Neuropsychological Society, 9(7). doi:10.1017/S135561770397010X

Delis, D. C, Kaplan, E, & Kramer, J. H. (2001). Delis–kaplan executive function system. New York: Psychological Corporation.

Destrieux, C., Hommet, C., Domengie, F., Boissy, J.-M., de Marco, G., Joanette, Y., … Cottier, J.-P. (2012). Influence of age on the dynamics of fMRI activations during a semantic fluency task. Journal of Neuroradiology. Journal De Neuroradiologie, 39(3), 158–166. doi:10.1016/j. neurad.2011.05.005

Diaz, M. T, Rizio, A. A, & Zhuang, J. (2016). The neural language systems that support healthy aging: integrating function, structure, and behavior. Language And Linguistics Compass, 10(7), 314–334. doi:10.1111/lnc3.v10.7

Donaldson, D.L., & Buckner, R.L. (2001). Effective paradigm design. In Donaldson, D.L., & Buckner, R.L. Functional mri, p (pp. pp. 177–193). Jezzard, ed. (Oxford: Oxford University Press.

Elvevåg, B., Fisher, J. E., Gurd, J. M., & Goldberg, T. E. (2002). Semantic clustering in verbal fluency: Schizophrenic patients versus control participants. Psychological Medicine, 32, 5.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state. A Practical Method for Grading the Cognitive State of Patients for the Clinician. Journal of Psychiatric Research, 12(3), 189–198.

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J.-P., Frith, C. D., & Frackowiak, R. S. J. (1994). Statistical parametric maps in functional imaging: A general linear approach. Human Brain Mapping, 2(4), 189–210.

Gierski, F., & Ergis, A.-M. (2004). Les fluences verbales: Aspects théoriques et nouvelles approches. L'année Psychologique, 104(2), 331–359.

Glikmann-Johnston, Y., Oren, N., Hendler, T., & Shapira-Lichter, I. (2015). distinct functional connectivity of the hippocampus during semantic and phonemic fluency. Neuropsychologia, 69, 39– 49. doi:10.1016/j.neuropsychologia.2015.01.031

Goñi, J., Arrondo, G., Sepulcre, J., Martincorena, I., Vélez de Mendizábal, N., Corominas-Murtra, B., … Villoslada, P. (2010). The semantic organization of the animal category: Evidence from semantic verbal fluency and network theory. Cognitive Processing. doi:10.1007/s10339-010-0372-x

Goulet, P., Joanette, Y., Sabourin, L., & Giroux, F. (1997). Word fluency after a right-hemisphere lesion. Neuropsychologia, 35(12), 1565–1570.

Grady, C. (2012). The cognitive neuroscience of ageing. Nature Reviews Neuroscience, 13(7), 491–505.

Grady, C. L. (1999). The effects of age on the neural correlates of episodic encoding. Cerebral Cortex, 9(8), 805–814.

Greenwood, P. M. (2007). Functional plasticity in cognitive aging: Review and hypothesis. Neuropsychology, 21(6), 657–673.

Greenwood, P. M., & Parasuraman, R. (2010). Neuronal and cognitive plasticity: A neurocognitive framework for ameliorating cognitive aging. Frontiers in Aging Neuroscience, 2(NOV), 1–14.

Gurd, J. M. (2002). Posterior parietal cortex is implicated in continuous switching between verbal fluency tasks: An fMRI study with clinical implications. Brain, 125(5), 1024–1038. doi:10.1093/ brain/awf093

Hazlett, E. A., Buchsbaum, M. S., & Mohs, R. C., Spiegel-Cohen, J., Wei, T. C., Azueta, R., Haznedar, M. M., Singer, M. B., Shihabuddin, L., Luu-Hsia, C., Harvey, P. D. (1998). Age-related shift in brain region activity during successful memory performance. Neurobiology of Aging, 19(5), 437–45. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9880046

Hedden, T., & Gabrieli, J. D. E. (2004). Insights into the ageing mind: A view from cognitive neuroscience. Nature Reviews. Neuroscience, 5(2), 87–96. doi:10.1038/nrn1323

Henry, J. D., Crawford, J. R., & Phillips, L. H. (2004). Verbal fluency performance in dementia of the Alzheimer's type: A meta-analysis. Neuropsychologia, 42(9), 1212–1222.

Hills, T. T, Todd, P. M, & Goldstone, R. L. (2008). Search in external and internal spaces. Psychological Science, 19(8), 802–808. doi:10.1111/j.1467-9280.2008.02160.x

Hills, T. T., Todd, P. M., & Goldstone, R. L. (2010). The Central Executive as a Search Process: Priming Exploration and Exploitation Across Domains. Journal of Experimental Psychology: General, 139 (4), 590–609. doi:10.1037/a0020666

Hirshorn, E. A., & Thompson-Schill, S. L. (2006). Role of the left inferior frontal gyrus in covert word retrieval: Neural correlates of switching during verbal fluency. Neuropsychologia, 44(12), 2547–2557. Ho, A. K., Sahakian, B. J., Robbins, T. W., Barker, R. A., Rosser, A. E., & Hodges, J. R. (2002). Verbal fluency in Huntington's disease: A longitudinal analysis of phonemic and semantic clustering and switching. Neuropsychologia, 40(8), 1277–1284.

Hoyau, E., Cousin, E., Jaillard, A., & Baciu, M. (2016). Modulation of the inter-hemispheric processing of semantic information during normal aging. A divided visual field experiment. Neuropsychologia, 93, 425–436.

Hughes, D. L., & Bryan, J. (2002). Adult age differences in strategy use during verbal fluency performance. Journal of Clinical and Experimental Neuropsychology, 24(5), 642–654. doi:10.1076/ jcen.24.5.642.1002

Hurks, P. P. M., Schrans, D., Meijs, C., Wassenberg, R., Feron, F. J. M., & Jolles, J. (2010). Developmental changes in semantic verbal fluency: Analyses of word productivity as a function of time, clustering, and switching. Child Neuropsychology, 16(4), 366–387.

Jessen, F, Amariglio, R. E, Van Boxtel, M, Breteler, M, Ceccaldi, M, Chételat, G, & Glodzik, L. (2014). A conceptual framework for research on subjective cognitive decline in preclinical alzheimer's disease. Alzheimer's & Dementia, 10(6), 844-852. doi: 10.1016/j.jalz.2014.01.001

Joanette, Y., Goulet, P., & Hannequin, D. (1990). The contribution of the right hemisphere to lexical semantics. In: Right hemisphere and verbal communication (pp. 42–115). New York: Springer- Verlag.

Jung-Beeman, M. (2005). Bilateral brain processes for comprehending natural language. Trends in Cognitive Sciences, 9(11), 512–518.

Kahlaoui, K., Di, S. G., Barbeau, J., Maheux, M., Lesage, F., Ska, B., & Joanette, Y. (2012). Contribution of NIRS to the study of prefrontal cortex for verbal fluency in aging. Brain and Language, 121(2), 164–173. doi:10.1016/j.bandl.2011.11.002

Kennedy, K. M., Rodrigue, K. M., Bischof, G. N., Hebrank, A. C., Reuter-Lorenz, P. A., & Park, D. C. (2015). Age trajectories of functional activation under conditions of low and high processing demands: An adult lifespan fMRI study of the aging brain. NeuroImage, 104, 21–34.

Koren, R., Kofman, O., & Berger, A. (2005). Analysis of word clustering in verbal fluency of school-aged children. Archives of Clinical Neuropsychology, 20(8), 1087–1104.

Kozora, E., & Cullum, C. M. (1995). Generative naming in normal aging: Total output and qualitative changes using phonemic and semantic constraints. The Clinical Neuropsychologist, 9(4), 313–320.

Kramer, A. F., Hahn, S., & Gopher, D. (1999). Task coordination and aging: Explorations of executive control processes in the task switching paradigm. Acta Psychologica, 101(2–3), 339–378.

Kramer, A. F., & Willis, S. L. (2002). Enhancing the cognitive vitality of older adults. Current Directions in Psychological Science, 11(5), 173–177.

Lacombe, J., Jolicoeur, P., Grimault, S., Pineault, J., & Joubert, S. (2015). Neural changes associated with semantic processing in healthy aging despite intact behavioral performance. Brain and Language, 149, 118–127.

Lanting, S., Haugrud, N., & Crossley, M. (2009). The effect of age and sex on clustering and switching during speeded verbal fluency tasks. Journal of the International Neuropsychological

Society : JINS, 15(2), 196–204.

Lezak, M. D., Howieson, D. B., & Loring, D. W. (2004). Neuropsychological assessment (4th ed. New York, NY: Oxford University Press.

Logan, J. M., Sanders, A. L., Snyder, A. Z., Morris, J. C., & Buckner, R. L. (2002). Under-recruitment and nonselective recruitment: Dissociable neural mechanisms associated with aging. Neuron, 33 (5), 827–840.

Lövdén, M., Bäckman, L., Lindenberger, U., Schaefer, S., & Schmiedek, F. (2010). A theoretical framework for the study of adult cognitive plasticity. Psychological Bulletin, 136(4), 659–676.

Markova, H, Andel, R, Stepankova, H, Kopecek, M, Nikolai, T, Hort, J, Thomas-Antérion, C, & Vyhnalek, M. (2017). Subjective cognitive complaints in cognitively healthy older adults and their relationship to cognitive performance and depressive symptoms. Journal Of Alzheimer's Disease, 59(3), 871–881. doi:10.3233/JAD-160970

Marsolais, Y., Methqal, I., & Joanette, Y. (2015). Marginal neurofunctional changes in high-perform- ing older adults in a verbal fluency task. Brain and Language, 140, 13–23.

Martin, R. C., Wu, D., Freedman, M., Jackson, E. F., & Lesch, M. (2003). An event-related fMRI investigation of phonological versus semantic short-term memory. Journal of Neurolinguistics, 16 (4–5), 341–360.

Martins, R., Simard, F., & Monchi, O. (2014). Differences between patterns of brain activity associated with semantics and those linked with phonological processing diminish with age. PLoS ONE, 9(6), e99710. doi:10.1371/journal.pone.0099710

Mata, R, & von Helversen, B. (2015). Search and the aging mind: the promise and limits of the cognitive control hypothesis of age differences in search. Topics In Cognitive Science, 7(3), 416– 427. doi:10.1111/tops.2015.7.issue-3

Mayr, U. (2002). On the dissociation between clustering and switching in verbal fluency: Comment on Troyer, Moscovitch, Winocur, Alexander and Stuss. Neuropsychologia, 40(5), 562–566.

Mayr, U., & Kliegl, R. (2000). Complex semantic processing in old age: Does it stay or does it go? Psychology and Aging, 15(1), 29–43.

McIntosh, A. R., Sekuler, A. B., Penpeci, C., Rajah, M. N., Grady, C. L., Sekuler, R., & Bennett, P. J. (1999). Recruitment of unique neural systems to support visual memory in normal aging. Current Biology, 9(21), 1275–S2.

Meinzer, M., Flaisch, T., Seeds, L., Harnish, S., Antonenko, D., Witte, V., … Crosson, B. (2012). Same modulation but different starting points: performance modulates age differences in inferior frontal cortex activity during word-retrieval. PLoS ONE, 7(3), e33631. doi:10.1371/journal.pone.0033631

Meinzer, M., Flaisch, T., Wilser, L., Eulitz, C., Rockstroh, B., Conway, T., … Crosson, B. (2009). Neural signatures of semantic and phonemic fluency in young and old adults. Journal of Cognitive Neuroscience, 21(10), 2007–2018. doi:10.1162/jocn.2009.21219

Monchi, O., Petrides, M., Strafella, A. P., Worsley, K. J., & Doyon, J. (2006). Functional role of the basal ganglia in the planning and execution of actions. Annals of Neurology, 59(2), 257–264.

Morcom, A. M., & Johnson, W. (2015). Neural reorganization and compensation in aging. Journal of Cognitive Neuroscience, 27(7), 1275–1285.

Muller, A. M., Mérillat, S., & Jäncke, L. (2016). Older but still fluent? Insights from the intrinsically active baseline configuration of the aging brain using a data driven graph-theoretical approach.

NeuroImage, 127, 346–362.

Mummery, C. J., Patterson, K., Hodges, J. R., & Wise, R. J. S. (1996). Generating "tiger" as an animal name or a word beginning with T: Differences in brain activation. Proceedings of the Royal Society B: Biological Sciences, 263(1373), 989–995.

Murray, B. D, Anderson, M. C, & Kensinger, E. A. (2015). Older adults can suppress unwanted memories when given an appropriate strategy. Psychology And Aging, 30(1), 9–25. doi:10.1037/ a0038611

Nagels, A., Kircher, T., Dietsche, B., Backes, H., Marquetand, J., & Krug, A. (2012). Neural processing of overt word generation in healthy individuals: The effect of age and word knowledge. NeuroImage, 61(4), 832–840.

Nikolai, T., Bezdicek, O., Markova, H., Stepankova, H., Michalec, J., Kopecek, M., Dokoupilova, M., Hort, J., Vyhnalek, M. (2017). Semantic verbal fluency impairment is detectable in patients with subjective cognitive decline. Applied Neuropsychology: Adult, 1–10. doi:10.1080/ 23279095.2017.1326047

Noonan, K. A., Jefferies, E., Visser, M., & Ralph, M. A. L. (2013). Going beyond inferior prefrontal involvement in semantic control : evidence for the additional contribution of dorsal angular gyrus and posterior middle temporal cortex. Journal of Cognitive Neuroscience, 25(11), 1824–1850.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the edinburgh inventory. Neuropsychologia, 9(1), 97–113. doi:10.1016/0028-3932(71)90067-4

Ollinger, J. M., Corbetta, M., & Shulman, G. L. (2001). Separating processes within a trial in event-related functional MRI. NeuroImage, 13(1), 218–229.

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., & Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. Psychology and Aging, 17 (2), 299–320.

Park, D. C., & McDonough, I. M. (2013). The dynamic aging mind. Perspectives on Psychological Science, 8(1), 62–67.

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: Aging and neurocognitive scaffolding. Annual Review of Psychology, 60(1), 173–196.

Park, D. C., Smith, A. D., Lautenschlager, G., Earles, J. L., Frieske, D., Zwahr, M., & Gaines, C. L. (1996). Mediators of long-term memory performance across the life span. Psychology and Aging, 11(4), 621–637. doi:10.1037/0882-7974.11.4.621

Parker, D.M., & Crawford, J.R, J.R. Crawford, D.M. Parker, & W.W. McKinley (Eds (1992). Assessment of frontal lobe function. In J.R. Crawford, D.M. Parker, & W.W. McKinley (Eds), A handbook of neuropsychological assessment. NJ : Lawrence Erlbaum: Hillsdale.

Peelle, J. E., Chandrasekaran, K., Powers, J., Smith, E. E., & Grossman, M. (2013). Age-related vulnerability in the neural systems supporting semantic processing. Frontiers in Aging Neuroscience, 5(SEP), 1–11.

Price, S. E, Kinsella, G. J, Ong, B, Storey, E, Mullaly, E, Phillips, M, & Perre, D. (2012). Semantic verbal fluency strategies in amnestic mild cognitive impairment. Neuropsychology, 26(4), 490–497. doi:10.1037/a0028567

Raboutet, C., Sauzéon, H., Corsini, M.-M., Rodrigues, J., Langevin, S., & N'Kaoua, B. (2010). Performance on a semantic verbal fluency task across time: Dissociation between clustering, switching, and categorical exploitation processes. Journal of Clinical and Experimental Neuropsychology, 32(3), 268–280. doi:10.1080/13803390902984464

Rajah, M. N., & D'Esposito, M. (2005). Region-specific changes in prefrontal function with age: A review of PET and fMRI studies on working and episodic memory. Brain, 128(9), 1964–1983. doi:10.1093/brain/awh608

Raskin, S. A., Sliwinski, M., & Borod, J. C. (1992). Clustering strategies on tasks of verbal fluency in Parkinson's disease. Neuropsychologia, 30(1), 95–99.

Regard, M. (1981). Cognitive rigidity and flexibility: A neuropsychological study (Unpublished Ph.D. dissertation.) University of Victoria, British-Columbia.

Reitan, R. M. (1971). Trail making test results for normal and brain-damaged children. Perceptual and Motor Skills, 33(2), 575–581.

Reuter-Lorenz, P. A. (2002). New visions of the aging mind and brain. Trends in Cognitive Sciences, 6

(9), 394–400.

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. Current Directions in Psychological Science, 17(3), 177–182.

Reuter-Lorenz, P. A., & Lustig, C. (2005). Brain aging: Reorganizing discoveries about the aging mind. Current Opinion in Neurobiology, 15(2), 245–251.

Robert, P. H., Lafont, V., Medecin, I., Berthet, L., Thauby, S., Baudu, C., & Darcourt, G. (1998). Clustering and switching strategies in verbal fluency tasks: Comparison between schizophrenics and healthy adults. Journal of the International Neuropsychological Society, 4, 6.

Rypma, B., Berger, J. S., & D'Esposito, M. (2002). The influence of working-memory demand and subject performance on prefrontal cortical activity. Journal of Cognitive Neuroscience, 14(5), 721–731. doi:10.1162/08989290260138627

Salthouse, T. A. (1988). Resource-reduction interpretations of cognitive aging. Developmental Review, 8(3), 238–272.

Salthouse, T. A., Fristoe, N., McGuthry, K. E., & Hambrick, D. Z. (1998). Relation of task switching to speed, age, and fluid intelligence. Psychology and Aging, 13(3), 445–461.

Sauzéon, H., Raboutet, C., Rodrigues, J., Langevin, S., Schelstraete, M. A., Feyereisen, P., . . . N'Kaoua, B. (2011). Verbal knowledge as a compensation determinant of adult age differences in verbal fluency tasks over time. Journal of Adult Development, 18(3), 144–154. doi:10.1007/s10804-010- 9107-6

Simard, F., Joanette, Y., Petrides, M., Jubault, T., Madjar, C., & Monchi, O. (2011). Fronto-striatal contribution to lexical set-shifting. Cerebral Cortex, 21(5), 1084–1093.

Simard, F., Monetta, L., Nagano-Saito, A., & Monchi, O. (2013). A new lexical card-sorting task for studying fronto-striatal contribution to processing language rules. Brain and Language, 125(3), 295–306.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. Journal of the International Neuropsychological Society, 8(3), 448–460. Stern, Y. (2009). Cognitive reserve. Neuropsychologia, 47(10), 2015–2028.

Sun, Y., Yang, F.-C., Lin, C.-P., & Han, Y. (2015). Biochemical and Neuroimaging Studies in Subjective Cognitive Decline: Progress and Perspectives. CNS Neuroscience & Therapeutics, 21(10), 768– 775. doi:10.1111/cns.12395

Talaraich, J., & Tournoux, P. (1988). Co-planar stereotaxic atlas of the human brain. Stuttgart: George Thieme.

Thompson, H. E., Henshall, L., & Jefferies, E. (2016). The role of the right hemisphere in semantic control: A case-series comparison of right and left hemisphere stroke. Neuropsychologia, 85, 44–61.

Tombaugh, T. (1999). Normative data stratified by age and education for two measures of verbal fluency FAS and animal naming. Archives of Clinical Neuropsychology, 14(2), 167–177.

Tröster, A. I., Fields, J. A., Testa, J. A., Paul, R. H., Blanco, C. R., Hames, K. A., … Beatty, W. W. (1998). Cortical and subcortical influences on clustering and switching in the performance of verbal fluency tasks. Neuropsychologia, 36(4), 295–304. 10.1016/S0028-3932(97)00153-X

Troyer, A. K. (2000). Normative data for clustering and switching on verbal fluency tasks. Journal of Clinical and Experimental Neuropsychology, 22(3), 370–378.

Troyer, A. K., Moscovitch, M., & Winocur, G. (1997). Clustering and switching as two components of verbal fluency: Evidence from younger and older healthy adults. Neuropsychology, 11(1), 138–146.

Troyer, A. K., Moscovitch, M., Winocur, G., Alexander, M. P., & Stuss, D. (1998). Clustering and switching on verbal fluency: The effects of focal frontal- and temporal-lobe lesions. Neuropsychologia, 36(6), 499–504.

Tyler, L. K., Shafto, M. A., Randall, B., Wright, P., Marslen-Wilson, W. D., & Stamatakis, E. A. (2010). Preserving syntactic processing across the adult life span: The modulation of the frontotemporal language system in the context of age-related atrophy. Cerebral Cortex, 20(2), 352–364.

Unsworth, N., Spillers, G. J., & Brewer, G. A. (2011). Variation in verbal fluency: A latent variable analysis of clustering, switching, and overall performance. The Quarterly Journal of Experimental Psychology, 64(3), 447–466.

Verhaegen, C., & Poncelet, M. (2013). Changes in naming and semantic abilities with aging from 50 to 90 years. Journal of the International Neuropsychological Society : JINS, 19(2), 119–126.

Visscher, K. M, Miezin, F. M, Kelly, J. E, Buckner, R. L, Donaldson, D. I, McAvoy, M. P, Bhalodia, V. M, & Petersen, S. E. (2003). Mixed blocked/event-related designs separate transient and sustained activity in fmri. Neuroimage, 19(4), 1694–1708. doi:10.1016/S1053-8119(03)00178-2

Wagner, A. D., Paré-Blagoev, E. J., Clark, J., & Poldrack, R. A. (2001). Recovering meaning. Neuron, 31(2), 329–338.

Whitney, C., Grossman, M., & Kircher, T. T. J. (2009). The influence of multiple primes on bottom-up and top-down regulation during meaning retrieval: Evidence for 2 distinct neural networks. Cerebral Cortex (New York, N.Y. : 1991), 19(11), 2548–2560.

Wierenga, C. E, Benjamin, M, Gopinath, K, Perlstein, W. M, Leonard, C. M, Rothi, Leslie J. Gonzalez, Conway, T, Cato, M. A, Briggs, R, & Crosson, B. (2008). Age-related changes in word retrieval: role of bilateral frontal and subcortical networks. Neurobiology Of Aging, 29(3), 436–451. doi:10.1016/ j.neurobiolaging.2006.10.024

Wingfield, A., & Grossman, M. (2006). Language and the aging brain: Patterns of neural compensation revealed by functional brain imaging. Journal of Neurophysiology, 96(6), 2830–2839.

Worsley, K. J. (2005). An improved theoretical P value for SPMs based on discrete local maxima. NeuroImage, 28(4), 1056–1062.

Worsley, K. J., Liao, C. H., Aston, J., Petre, V., Duncan, G. H., Morales, F., & Evans, A. C. (2002). A general statistical analysis for fMRI data. NeuroImage, 15(1), 1–15.

Zakzanis, K. K., McDonald, K., & Troyer, A. K. (2013). Component analysis of verbal fluency scores in severe traumatic brain injury. Brain Injury : [BI], 27(7–8), 903–908.

Zhang, W., Wang, J., Fan, L., Zhang, Y., Fox, P. T., Eickhoff, S. B., … Jiang, T. (2016). Functional organization of the fusiform gyrus revealed with connectivity profiles. Human Brain Mapping, 37 (8), 3003–3016

Table 1 : Means (M) and standard deviations (SD) of the demographic and neuropsychological variables of the participants (n = 26).

	Younger adults (n = 13)	**Older adults (n = 13)**	T-test t(24)
	M (SD)	M (SD)	
Age (years)	24.23 (3.19)	63.23 (3.58)	-26.47**
Education (years)	16 (1.68)	17.23 (2.48)	-1.47
Gender (F: M)	6/7	7/6	0.38
MMSE	29.77 (1.53)	29.54 (0.66)	1.05
Edinburgh inventory (%)	94.61 (5.18)	95.38 (5.18)	-0.38
Stroop Victoria test			
Color-word (time in seconds)	16.85 (4.45)	29.88 (11.91)	-3.69**
Color-word (errors)	0.08 (0.27)	0.85 (1.4)	-1.93
Inhibition score[a]	0.18 (0.14)	0.32 (0.14)	-2.33*
Trail Making test			
TMT B (time in seconds) [b]	40.31 (8.23)	76 (14.88)	-7.56**
TMT B (errors)	0.08 (0.27)	0.46 (0.66)	-1.93
Alpha Span			
Serial recall	6.23 (1.87)	5.23 (1.53)	1.48
Alphabetical recall[c]	3.30 (1.97)	2.61 (1.85)	0.92
Executive score[d] (z)	1.14	-0,15	2.08*

Note: * p<.05; **p<.01

[a] The score inhibition was computed as: (inhibition time condition (color-word) – Naming time condition (color)/ (inhibition time condition (color-word) + Naming time condition (color) (Park et al., 1996; Sauzéon et al., 2010)

[b] cognitive flexibility measure.

[c] Total number of correct alphabetical recalls for each same sequence (max. score=10) reflecting ability to maintain and manipulate verbal information in working memory.

[d] The average of standardized executive z-score collapsed across three cognitive measures: inhibition, cognitive flexibility and working memory.

Table 2 : Strategic components of semantic and orthographic verbal fluency performance for the participants.

	Younger adults	Older adults	T-test
	M (SD)	M (SD)	t24
Semantic[a]			
Number of words produced	88.30 (16.66)	79.76 (17.54)	1.27
Mean cluster size[b]	1.88 (0.26)	2.20 (0.41)	-2.32*
Number of Clusters	6.38 (1.47)	5.30 (1.22)	2.01
Number of Switches[c]	9.21 (1.55)	9 (2.21)	0.28
Orthographic[a]			
Number of words produced	82.15 (23.09)	83.61 (25.30)	0.15
Mean cluster size[b]	1.59 (0.41)	1.86 (0.70)	-1.17
Number of Clusters	6.01 (2.05)	6 (2.13)	0.02
Number of Switches[c]	10.34 (2.08)	11.15 (3.51)	-0.71

Note: * p<.05

[a] four criteria of each fluency task are combined.

[b] Larger clustering scores reflect increased cluster size

[c] Larger switching scores reflect a higher frequency of switches.

Table 3 : Semantic clustering minus control condition

	Stereotaxic coordinates				
Anatomical areas	**x**	**y**	**z**	**t-Values**	**Cluster size**
Younger					
Ventrolateral prefrontal cortex (area 45)					
Left	-42	22	22	5.14	>10000
Dorsolateral prefrontal cortex (area 9/46)					
Left	-48	18	28	4.66	>10000
Anterior cingulate cortex (area 32)					
Left	-10	16	30	4.36	>10000
Right	18	24	24	4.87	>10000
Superior frontal cortex (area 6,8, SMA)					
Left	-2	10	52	7.65	>10000
Right	8	4	64	4.57	>10000
Lateral posterior prefrontal cortex (area 8)					
Left	-26	4	52	5.77	>10000
Lateral premotor cortex (area 6)					
Left	-34	-4	62	5.2	>10000
Posterior inferior parietal cortex (area 40)					
Left	-38	-48	40	3.99	968
Superior temporal cortex (area 22)					
Right	50	-36	6	4.57	1488
Caudate nucleus					
Left	-18	4	16	5.34	>10000
Right	20	14	12	4.54	>10000
Putamen					
Left	-20	4	-2	4.44	>10000
Right	24	6	2	3.62	>10000
Thalamus					

Left	-4	-8	6	4.72	>10000
Right	6	-8	2	4.29	>10000
Cerebellum					
Left	-10	-76	-18	4.45	5408
Right	30	-64	-26	4.25	5408

Tableau 3 cont.

	Stereotaxic coordinates				
Anatomical areas	**x**	**y**	**z**	**t-Values**	**Cluster size**
Older					
Superior frontal cortex (area 6,8, SMA)					
Left	-4	8	54	6.47	3688
Right	32	12	52	4.36	928
Lateral posterior prefrontal cortex (area 8)					
Left	-26	8	52	4.75	1448
Right	38	12	34	4.15	696
Posterior prefrontal cortex (junction of 6, 8, and 44)					
Left	-40	8	26	4.02	1440
Middle temporal cortex (area 21)					
Right	66	-42	-14	4.22	664
Inferior temporal cortex (area 37, Fusiform)					
Left	-50	-46	-18	4.24	1320
Right	58	-42	-14	3.88	664
Occipital cortex (area 17)					
Left	-2	-76	-6	4.03	256
Younger > Older					
Posterior cingulate cortex (area 23)					

Right	16	-20	32	3.80	544
Inferior temporal cortex (are 38)					
Left	-32	-8	-42	4.40	1120
Older > Younger					
Inferior temporal cortex (area 37)					
Right	64	-40	-18	3.79*	224

[*] uncorrected at p<0.001

Table 4 : Correlation of the evolution of the BOLD signal during semantic clustering.

	Stereotaxic coordinates				
Anatomical areas	**x**	**y**	**z**	**t-Values**	**Cluster size**
Younger					
Anterior cingulate cortex (areas 32/24)					
Left	-12	16	34	3.4	4312
Right	16	18	30	3.85	512
Lateral posterior prefrontal cortex (area 8)					
Left	-6	12	52	4.58	4312
Superior frontal cortex (area 6,8, SMA)					
Left	-4	2	66	4.18	4312
Right	8	-2	70	3.61	4312
Posterior prefrontal cortex (junction of 6, 8, and 44)					
Left	-30	4	48	4.69	2048
Lateral premotor cortex (area 6)					
Left	-34	-8	36	4.07	392
Putamen					
Left	-20	-2	18	4.65	2912
Caudate nucleus					
Left	-12	-6	16	3.9	2912
Cerebellum cortex					

Right	42	-66	-26	4.51	7664
Older					
Lateral posterior prefrontal cortex (area 8)					
Left	-6	10	52	4.03	208
Inferior temporal cortex (area 37, Fusiform)					
Left	-50	-44	-18	3.40*	120
Cerebellum cortex					
Right	22	-70	-44	3.90	384

[*] uncorrected at p<0.001. SMA: supplementary motor area

Table 5 : Semantic switching minus control condition

	Stereotaxic coordinates				
Anatomical areas	**x**	**y**	**z**	**t-Values**	**Cluster size**
Younger					
Ventrolateral prefrontal cortex (area 44/45)					
Left	-46	36	12	4.15	6960
Dorsolateral prefrontal cortex (area 9/46)					
Left	-50	20	30	4.55	6960
Superior frontal cortex (area 6,8, SMA)					
Left	-42	2	28	4.92	6960
Older					
Superior frontal cortex (area 6,8, SMA)					
Left	-6	8	52	4.06	264
Inferior temporal cortex (area 37, Fusiform)					
Left	-56	-46	-18	3.50	96
Younger > Older					
Caudate nucleus					
Right	10	10	16	3.62	432
Older > Younger					
Middle temporal cortex (area 20)					
Left	56	2	-36	4.64	488

SMA : supplementary motor area

Table 6 : Orthographic clustering minus control condition

	Stereotaxic coordinates				
Anatomical areas	**x**	**y**	**z**	**t-Values**	**Cluster size**
Younger					
Ventrolateral prefrontal cortex (area 44/45)					
Left	-46	34	10	4.32	>10000
Anterior cingulate cortex (area 32)					
Left	-2	18	38	3.77	>10000
Posterior prefrontal cortex (junction of 6, 8, and 44)					
Left	-46	4	28	5.76	>10000
Superior frontal cortex (area 6,8, SMA)					
Left	-2	10	54	6.2	>10000
Right	12	6	56	3.81	>10000
Posterior inferior parietal cortex (area 40)					
Left	-32	-48	40	4.74	1184
Caudate nucleus					
Left	-14	-6	16	4.03	968
Older					
Ventrolateral prefrontal cortex (area 47/12)					
Left	-46	26	0	3.95	536
Posterior prefrontal cortex (junction of 6, 8, and 44)					
Left	-46	8	24	5.77	6032
Superior frontal cortex (area 6,8, SMA)					
Left	-8	6	54	5.29	6464
Right	6	12	56	4.02	6464
Posterior inferior parietal cortex (area 40)					
Left	-36	-44	40	3.82	864
Inferior temporal cortex (area 37, Fusiform)					

Left	-56	-46	-18	5.15	2840
Younger > Older					
Middle temporal cortex (are 21)					
Right	34	-50	2	4.58	608
Inferior temporal cortex (area 37)					
Left	-36	-8	-40	4.29	376
Older > Younger					

SMA : supplementary motor area

Table 7 : Orthographic switching minus control condition

	Stereotaxic coordinates				
Anatomical areas	**x**	**y**	**z**	**t-Values**	**Cluster size**
Younger					
Ventrolateral prefrontal cortex (area 44/45)	-44	34	8	5.34	>10000
Left					
Dorsolateral prefrontal cortex (area 9/46)	-42	24	22	4.95	>10000
Left					
Ventrolateral prefrontal cortex (47/12)					
Left	-30	16	6	4.14	1144
Posterior prefrontal cortex (area 44)					
Left	-48	14	24	4.81	>10000
Anterior cingular cortex (area 32)					
Left	-6	12	46	5.08	>10000
Right	16	16	30	4.40	>10000
Superior frontal cortex (area 6,8, SMA)					
Left	-8	2	64	5.22	>10000
Lateral posterior prefrontal cortex (area 8)					
Left	-36	-4	58	4.38	>10000
Middle temporal cortex (area 21)					
Left	-56	-34	2	3.82	600
Caudate nucleus					
Left	-14	-4	18	4.46	3240
Thalamus					
Left	-4	-10	6	3.91	3240
Older					
Posterior prefrontal cortex (junction of 6, 8, and 44)					
Left	-42	10	26	5.06	3544
Superior frontal cortex (area 6,8, SMA)					

Left	-6	6	56	5.49	6240
Right	6	20	50	3.66	6240
Lateral premotor cortex (area 6)					
Left	-26	4	46	4.04	6240
Inferior temporal cortex (area 20)					
Left	-48	-40	-20	5.06	2024
Younger > Older					
Anterior cingulate cortex (area 32)					
Left	-18	46	2	4.56	432
Older > Younger					
Posterior prefrontal cortex (area 6/8)					
Right	24	0	52	3.28	272

SMA : supplementary motor area

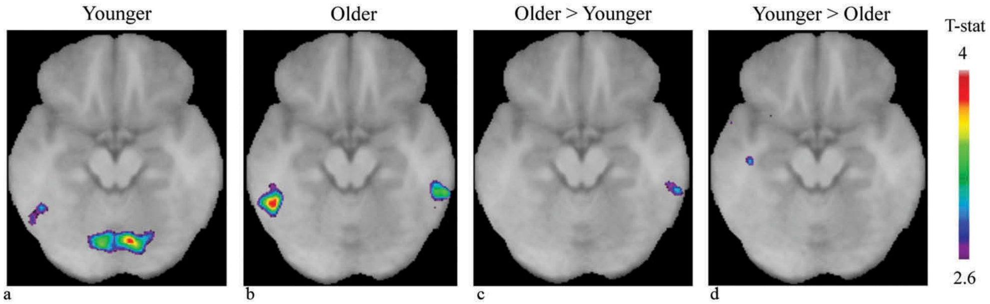

Figure 1. Activation for semantic clustering minus control condition. Horizontal section through the right inferior temporal cortex (area 37) peaks at $Z = -18$. The average of functional activity is superimposed on the anatomical MRI which is the average of the T1 acquisitions of the 13 younger adults and the 13 older adults transformed into the Montreal Neurological Institute (MNI) standard proportional stereotaxic space. The color scale represents the T statistic. (A) Activity for the younger adults. (B) Activity for the older adults. (C) Activity for the older adults compared to the younger adults (uncorrected at $p < 0.001$). (D) Activity for the younger adults compared to the older adults.

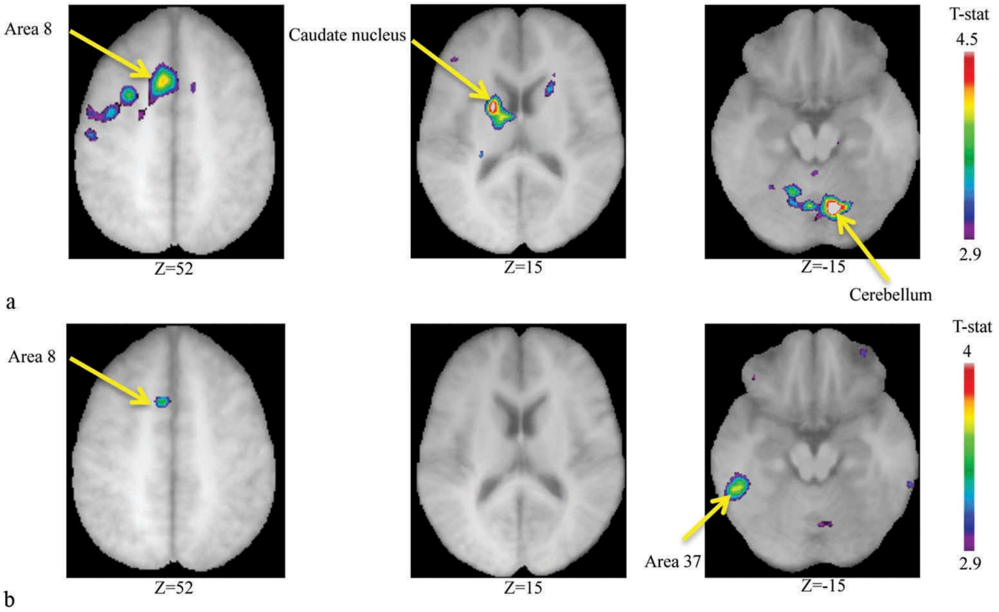

Figure 2. Correlation between BOLD signal changes and word production within the semantic cluster for the younger and older adults. The average of functional activity is superimposed on the anatomical MRI which is the average of the T1 acquisitions of the 13 younger adults and the 13 older adults transformed into the Montreal Neurological Institute (MNI) standard proportional stereotaxic space. The color scale represents the T statistic. (A) The younger adults showed significant activation in the left lateral posterior prefrontal cortex (Area 8), the left caudate nucleus and the right cerebellum. (B) The older adults showed significant activation in the left inferior temporal cortex (area 37).

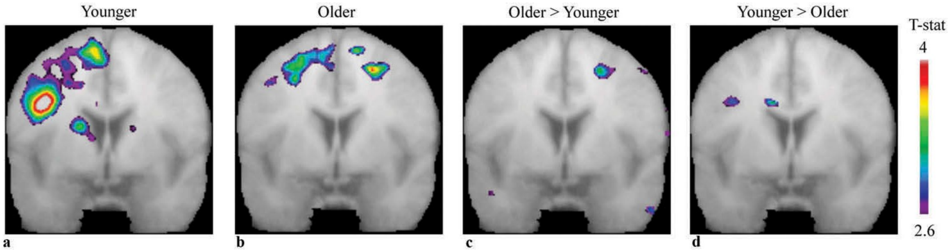

Figure 3. Activation for orthographic switching minus control condition. Coronal section through the right posterior prefrontal cortex (area 6/8) peaks at Y = 0. The average of functional activity is superimposed on the anatomical MRI which is the average of the T1 acquisitions of the 13 younger adults and the 13 older adults transformed into the Montreal Neurological Institute (MNI) standard proportional stereotaxic space. The color scale represents the T statistic. (A) Activity for the younger adults. (B) Activity for the older adults. (C) Activity for the older adults compared to the younger adults. (D) Activity for the younger adults compared to the older adults.

Supplementary material

Catégorie : Animaux

Lieu de vie

Afrique	Amérique du Nord/Pôle Nord	Australie/Asie
Autruche, crocodile, mangouste, porc-épic, rhinocéros, lion, tigre, éléphant, mammouth, girafe, zèbre, gazelle, antilope, hyène, lynx, panthère, jaguar, léopard, singe, orang outan, chimpanzé, gorille, bonobo, babouin, lémur, bison, hippopotame, chameau, dromadaire, etc.	Ours, grizzly, kodiak, carcajou, chevreuil, orignal, cerf, wapiti, biche, daine, caribou, renne, élan, lama, marmotte, écureuil, moufette, raton-laveur, martre, loutre, castor, belette, marmotte, moufette, harfang des neiges, renard, loup, coyote, ours polaire, ours blanc ou polaire, cougar, puma, etc.	Kangourou, koala, panda, chameau, éléphant, jaguar, porc-épic, rhinocéros, tigre, mangouste, ornithorynque, gibbon, orang-outan, etc.

Mode de vie

Aquatique	Reptiles	Oiseau/Insecte	Rongeurs	Bête de somme	Ferme	De compagnie	Fable de la Fontaine et association sémantique
Requin, dauphin, baleine, cachalot, truite, saumon, doré, calmar, mollusque, anguille, pieuvre Ornithorynque Grenouille, crapaud, triton, salamandre Loutre	Crocodile, alligator, iguane, salamandre, lézard Serpent, boa, anaconda, couleuvre, python Tortue, etc.	Aigle, autruche, perruche, perroquet, canari, merle, pic bois, carouge, étourneau, perdrix, moineau, colombe, pigeon, corneille, mésange, bouvreuil, paon, canard, coq, poule, colibri, sitelle, pintade, dindon, dinde, martin pêcheur, harfang des neiges, hibou, cardinal, cigogne, mouette, toucan, flamant rose, corbeau, chauve-souris, geai bleu, serin, oie	Raton-laveur, castor, porc épic, rat, souris, dègue, hamster, gerbille, lièvre, lapin, chinchilla, rat-musqué, ragondin, etc.	Lama, cheval, âne, chameau, mule, bison, taureau, mule, mulet, etc.	Âne, cheval, mule, mulet, taureau, bœuf, vache, mouton, agneau, brebis, bélier, bison, chèvre, cochon, truie, sanglier, pécari, coq, poule, dinde, canard, oie, chat, chien, renard*, paon, pintade, dindon, dinde, perdrix, etc.	Chat, chien, canari, perruche, perroquet, hamster, furet, cochon d' inde, furet, poisson rouge, tortue, etc.	Corbeau/renard Lièvre/tortue Cigale/fourmi Loup/agneau Chat/souris Chat/chien Grenouille/bœuf Couleuvre/mulot

Allure

Bœuf, bison, taureau, vache, veau, etc.	**Chameau, dromadaire, lama, etc.**	**Chacal, coyote, loup, renard, chien, etc.**
Bouquetin, chamois, chèvre, mouflon, mouton, etc.	Biche, caribou, cerf, chevreuil, daim, élan, faon, renne, wapiti, etc.	Couguar, guépard, jaguar, léopard, lion, lynx, panthère, puma, tigre, chat, etc.
Crabe, crevette, écrevisses, homard, langouste, etc.	Calmar, poulpe, escargot, pieuvre, huitre, moule, etc.	Belette, blaireau, fouine, furet, hermine, loutre, martre, putois, vison, raton-laveur, ragondin, mangouste, etc.
Babouin, chimpanzé, gorille, macaque, orang-outang, bonobo, gibbon, etc.	Porc-épic, hérisson, etc.	Âne, mule, mulet, cheval, zèbre, etc.

Catégorie : Légumes

Tiges/fleurs/feuilles			Fruit de plantes		Sous-terre	
Tiges	**Fleurs**	**Feuilles**	**Graines**	**Courges**	**Bulbe**	**Racine/tubercule**
Asperge, cèleri, rhubarbe, poireau, salsifis, cardon, fenouil, etc.	Artichaut, brocoli, brocofleur, chou, chou de Bruxelles, chou-fleur, endives, etc.	Épinard, laitue, mâche, côte de blette, chèvrefeuille, pissenlit, salade, poireau, cardon, luzerne, chicoré, fenouil, persil, sauge, etc.	Haricot, mais, pois, pois chiche, fève, blé d' inde, petits pois, mange tout, lentilles, flageolets, etc.	Potiron, citrouille, courge musquée, zucchini ou courgette, concombre, cornichon, tomate, avocat, aubergine, piment poivron, etc.	Ail, échalote, oignon, Poireau, fenouil, etc.	Betterave, carottes, navet, panais, rutabaga, pomme de terre, patate douce, topinambour, radis, céleri, endives, chicoré, etc.

Catégorie : Sport

À balle	Aquatique	Glisse/neige/glace	Olympique
Football, baseball, soccer, handball, basketball, badminton, tennis, golf, water-polo, rugby, cricket, soft-ball, hockey, polo, la crosse, rink-hockey, beach-volley, ballon-balai, curling, pétanque, squash, etc.	Natation, plongeon, natation synchronisée, aviron, canoë-kayak, planche à voile, ski nautique, water-polo, rafting, surf, voile, plongée, jet ski, etc.	Ski de fond, luge, bobsleigh, snowboard, ski alpin, raquette à neige, surf des neiges, roller, skateboard, hockey, curling, rink-hockey, ballon-balai, etc.	Tir à l'arc, tir, escrime, course, marche rapide, relais, saut en longueur, saut en hauteur, lancer de poids, lancer de javelot, natation, plongeon, lancer de poids, natation, cyclisme, haltérophilie, gymnastique, danse, etc.
Combats/arts martiaux	**Mécanique**	**Activité nature**	**Activité aérienne**
Judo, boxe, lutte, karaté, taekwondo, Yoga, etc.	Course automobile, jet ski, motocross, motocyclisme, etc.	Rafting, trekking, escalade, canoë-kayak, marche, raquette, chasse, pêche, etc.	Parachutisme, pilotage, delta plane, parapente, etc.

Catégorie: Vêtements

Tête/cou	Dessus du corps	Bassin/lingerie
Tuque, chapeau, casquette, capeline, châle, bonnet, foulard, écharpe, passe-montagne, capeline, bonnet, cagoule, etc.	Veste, manteau, imperméable, gilet, camisole, tee-shirt, chemise, débardeur/pull-over, polo, chandail, Poncho, parka, kangourou, coton ouaté, capuchon, cardigan, tunique, redingote, chemise, chemisier, blouse, tablier, paletot, corset, brassière, etc.	Soutien-gorge, boxer, bobette, brassière, culotte, short, slip, bermuda, bustier, collants, corsage, guêpière, etc.

Pieds	**Saison/Tenue**	**Accessoires**
Chaussettes, chaussures, sandales, bottes, tongs, mocassins, etc.	Manteau, gant, mitaine, pull, short, sandale, tee-shirt, casquette, survêtement, basket, chaussettes, costume, tailleur, robe, blazer, cravate, etc.	Capeline, châle, bonnet, foulard, écharpe, passe-montagne, cagoule, moufles, mitaine, gants, ceinture, cravate, nœud de papillon, etc.

Jambes	**Tenue de nuit**	**Associations diverses plus fréquentes**
Jeans, pantalon, capri, robe, jupe, collants, bas, etc.	Chemise de nuit, nuisette, pyjama, robe de chambre, etc.	Torse/jambes, torse/accessoires, etc.

CHAPITRE IV : ARTICLE 2

Age-Related Shift in Neuro-Activation during a Word-Matching Task

Ikram Methqal[1,2*], Jean-Sebastien Provost[3], Maximiliano A. Wilson[4], Oury Monchi[5], Mahnoush Amiri[1], Basile Pinsard[2], Jennyfer Ansado[6] and Yves Joanette[1,2]

1 Laboratory of Communication and Aging, Institut Universitaire de Gériatrie de Montréal, Montreal, QC, Canada, 2 Faculty of Medicine, University of Montreal, Montreal, QC, Canada, 3 Helen Wills Neuroscience Institute, University of California, Berkeley, Berkeley, CA, United States, 4 Centre de Recherche CERVO – CIUSSS de la Capitale-Nationale et Département de Réadaptation, Université Laval, Québec City, QC, Canada, 5 Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada, 6 Department of Psychology, Université du Québec en Outaouais, Gatineau, QC, Canada.

Publié dans la revue

Frontiers in Aging Neurosciences

Contribution des auteurs

Ikram Methqal: conceptualisation de l’étude et de la méthodologie, recrutement de participants, expérimentation, passation des tests neuropsychologiques, passation session d’IRMf, préparation, extraction, analyse et interprétation des données IRMf, comportementales et neuropsychologiques, rédaction du manuscrit

Jean-Sebastien Provost: participation à la conceptualisation de la méthodologie, révision d’une partie de la méthodologie

Maximiliano A. Wilson: validation de la des données comportementales de l’étude pilote, et révision de l’article

Oury Monchi: élaboration du logiciel de programmation de la méthodologie et de l’analyse des données IRMf, révision de la méthodologie

Mahnoush Amiri: révision critique de la méthodologie IRMf et revision de l’article

Basile Pinsard: élaboration d’une nouvelle méthodologie d’analyse des données IRMf et revision de l’article.

Jennyfer Ansado: participation à une discussion sur les données IRMf

Yves Joanette: directeur de recherche, conceptualisation de l’étude et de la méthodologie, interprétation des résultats et révision du manuscrit

Abstract

Growing evidence from the neuroscience of aging suggests that executive function plays a pivotal role in maintaining semantic processing performance. However, the presumed age-related activation changes that sustain executive semantic processing remain poorly understood. The aim of this study was to explore the executive aspects of semantic processing during a word-matching task with regard to age-related neuro-functional reorganization, as well as to identify factors that influence executive control profiles. Twenty younger and 20 older participants underwent fMRI scanning. The experimental task was based on word-matching, wherein visual feedback was used to instruct participants to either maintain or switch a semantic-matching rule. Response time and correct responses were assessed for each group. A battery of cognitive tests was administrated to all participants and the older group was divided into two subgroups based on their cognitive control profiles. Even though the percentage of correct responses was equivalent in the task performance between both groups and within the older groups, neuro-functional activation differed in frontoparietal regions with regards to age and cognitive control profiles. A correlation between behavioral measures (correct responses and response times) and brain signal changes was found in the left inferior parietal region in older participants. Results indicate that the shift in age-related activation from frontal to parietal regions can be viewed as another form of neuro-functional reorganization. The greater reliance on inferior parietal regions in the older compared to the younger group suggests that the executive control system is still efficient and sustains semantic processing in the healthy aging brain. Additionally, cognitive control profiles underlie executive ability differences in healthy aging appear to be associated with specific neuro-functional reorganization throughout frontal and parietal regions. These

findings demonstrate that changes in neural support for executive semantic processing during a word-matching task are not only influenced by age, but also by cognitive control profile.

1 INTRODUCTION

Healthy aging is accompanied by changes in numerous cognitive abilities, with performance differences noted within and between cognitive domains (Valdois et al., 1990; Goh et al., 2012). For instance, slight age-related changes have been reported for cognitive abilities that involve semantic processing, which remains relatively stable across the lifespan (Burke and Shafto, 2004), unlike those abilities that have been shown to decline with age such as episodic memory, visual attention and inhibition (e.g. Park et al., 2002). However, these age-related cognitive changes are less extensive than one would expect, given age-related structural brain changes.

The preservation of cognitive performance in healthy aging is usually associated with adaptive changes in brain activity (Reuter-Lorenz and Cappell, 2008). One such neurofunctional change is the presence of more widespread activation involving both hemispheres in older adults, a phenomenon formalized in the HAROLD model (Hemispheric Asymmetry Reduction in Older Adults; Cabeza, 2002). In addition to inter-hemispheric neurofunctional symmetry, intra-hemispheric changes have been also described, such as the PASA phenomenon (Posterior-Anterior Shift with Aging; Davis et al., 2008). Interestingly, convergent findings from our laboratory and from other studies reflect that there is often an age-related activation shift from anterior to posterior regions to support cognitive performance (Ansado et al., 2013b; Lacombe et al., 2015). For instance, Ansado et al., (2013a) have reported an age-related additional parietal recruitment to cope with increasing cognitive demands during a load-dependent judgment task. Similarly, Oedekoven et al., (2013) have found a greater parietal activity contribution, which resulted in successful episodic memory retrieval among older individuals. Thus, the engagement of parietal regions at high-demanding tasks tends to reflect the neurofunctional reorganization within fronto-parietal networks that supports cognitive performance in healthy cognitive aging.

It is well known that one of the most important age-related changes in brain activation takes place in frontal regions that are known to be involved in executive (or cognitive) control processes (Grady, 2012; Paxton et al., 2008). Although one could assume, from the findings mentioned above, that these regions are not sufficient to explain all age-related differences in executive resources involved in maintaining task performance (Colette and Salmon, 2014; Bouaazaoui et al., 2014). Based on the most neuroimaging findings, changes in executive control functioning could be the first indicator of the brain's adaptation strategy to insufficient neural resources in healthy aging by flexible neural reallocation (Reuter-Lorenz and Cappell, 2008; Adrover-Roig and Barcelo, 2010). In one relevant neuroimaging study, Peelle et al., (2013) showed that older adults with better semantic processing tended to rely more on the prefrontal and inferior parietal regions for word-meaning judgment than younger adults or older adults with poorer semantic performance. These findings suggest that the executive control regions (i.e. frontal and parietal regions) constitute the neurofunctional basis for semantic performance maintenance in healthy aging.

From a cognitive perspective, cognitive control supports a variety of executive processes defined as the ability to maintain and update information in working memory and to switch from current information to the adoption of new information, which involve a higher level of executive control (Miyake et al., 2000; Braver et al., 2003; Adrover-Roig et al., 2012). There has been, however, relatively little investigation on age-related neuro-functional changes of neural patterns relevant to executive control processes in semantic tasks.

The relative preservation of semantic processing can be defined by the degree of control over maintaining and/or switching among different types of semantic word relationships (Nagel et al., 2008; Noonan et al., 2010; Maintenant et al., 2011; Whitney et al., 2012). Growing evidence is emerging from functional neuroimaging studies that have considered the interactions between the executive control and language networks (Whitney et al., 2011; Noonan et al., 2013; Lambon-Ralph et al., 2016). Consistent findings from these studies reveal the extent of executive control network activation for semantic performance in language comprehension tasks. These large neural networks underpinning semantic and executive processes consist of inferior prefrontal, anterior cingulate, inferior parietal and posterior temporal cortices, as well as the cerebellum (Bookheimer, 2002; Noppeney et al., 2004; Binder et al., 2009). For instance, prefrontal regions supporting executive control processes are specifically active for the effective use of relevant semantic knowledge as well as when manipulation of semantic relationships is required during retrieval and selection among semantically related competitor words (Thomson-Shill et al., 1997; Wagner et al., 2001; Badre and Wagner, 2007; Maintenant et al., 2013). In addition to this prefrontal involvement, inferior parietal regions were also consistently activated across semantic tasks with high level of executive control (Noonan et al., 2010; Whitney et al., 2012). However, it is unclear whether these age-related changes in the activation of cognitive control networks sustain the semantic processing of words or if such activation reveals some dynamic processes. Overall, we could claim that studying executive aspects of semantic words processing is particularly appropriate for exploring possible neurofunctional reorganization with age.

Considering the fronto-parietal network involvement in semantic tasks requiring executive control processes (Binder and Desai, 2011; Noonan et al., 2013; Peelle et al., 2013), the first goal of this study was to explore, behaviorally and neurofunctionally, the age-related activation changes in fronto-parietal regions that underlie executive aspects of semantic processing. More specifically, an original word-matching task was developed based on the executive requirements of the Wisconsin Card Sorting Test (WCST) and was adapted for use in fMRI protocols (Monchi et al., 2001). This task requires the flexible use of semantic relationship (or rules) supported by two executive processes: (a) maintain rule; and (b) switch rule. The first process requires participants to maintain a given semantic rule through working memory updates, while the second one requires a shift from one rule to another. The latter is related to higher-level of executive control relative to the former.

Given the neurofunctional changes that occur concomitantly with the relative preservation of semantic ability in healthy aging (Ansado et al., 2013a; Peelle et al., 2013; Lacombe et al., 2015), we expected that older adults show greater activation in the inferior parietal regions, relative to younger adults. More precisely, these age-related neurofunctional changes were expected at the higher-level of executive control process necessary for the switch rule rather than for the maintain rule. Finally, it was expected that behavioral performance differences, measured by response times and correct responses, would be correlated with brain activation changes for both groups.

A current issue in cognitive aging studies is the reorganization of executive processes that occurs in contribution to age-related changes performance in complex executive tasks. In the past decade of cognitive aging studies, many researchers have supported the idea of the non-unitary nature of executive functions in healthy aging (Hull et al., 2008; Adrover-Roig et al., 2012), unlike those who have focused on a single and common executive system in aging (de Frias et al., 2006). These claims might further be viewed as extending work of Miyake et al., (2000) by supporting the notion that age-related changes in executive performance could be better explained by diversity in executive functions represented by at least two distinct executive subcomponents, though they are not completely independent. These executive processes consist of updating and maintaining information in working memory, and shifting between mental sets. Such distinction has also been found at the level of the neurofunctional organizations between updating and shifting processes, the former process supported by the activation of prefrontal regions, while the latter being mainly associated with parietal regions engagement (e.g. Collette et al., 2006; Braver et al., 2009; Herd et al., 2014; Kopp et al., 2014).

These executive processes are defined as distinct executive subcomponents that are differentially used by older adults. Some findings have further highlighted that higher level of global cognitive functioning would be associated with largely separable executive control processes (Adrover-Roig and Barceló, 2010; Collette and Salmon, 2014). In this context, de Frias et al., (2006) have reported that high cognitive functioning in older adults is related to highly differentiated executive control processes rather than unitary process. Moreover, Adrover-Roig et al., (2012) have found neurofunctional changes that are associated with the level of cognitive control in older adults. In that study, older adults with low level of cognitive control showed less activation in frontal regions indicating inefficiency in updating/maintaining processing compared to older adults with high level of cognitive control. As the existence of changes in executive function among older adults is supported by distinct executive control processes underpinned by neurally-distributed networks, the second goal of this study was to explore whether different cognitive control profiles in aging would correspond to specific neurofunctional reorganization patterns.

Based on different cognitive measures that encompass executive (or cognitive) control processes, we aimed to identify if a) at a behavioral level, individual differences in executive performance could be triggered by different cognitive control profile (updating-specific and shifting-specific) among older adults; and b) at a neurofunctional level, neurofunctional reorganization patterns are associated to specific cognitive control profiles. More specifically, the possibility that central cognitive control processes may be linked to specific cognitive profiles was examined in elderly people. It was expected that older adults with a shifting-specific profile would rely more extensively on parietal regions, while the updating-specific profile would recruit more frontal regions to maintain the performance to a given task. Finally, it was also expected that there would be a correlation between behavioral performance (response times and correct responses) and task-induced brain activation changes in each cognitive profile within an elderly group.

2 MATERIALS AND METHODS

2.1 Participants

Twenty healthy older adults aged between 63 and 80 and 20 younger adults whose ages ranged from 19 to 35 were recruited from a pool of volunteers at the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM). All participants were native French speakers and all were right-handed (scores greater than +95) as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). All had normal or corrected-to-normal vision; none had any history of major neurological disease, psychiatric illness, head injury, stroke, substance abuse, learning disabilities, or any problems that could interfere with behavior testing. Prior to the neuroimaging session, all participants were also given a battery of neuropsychological tests during a single 90-minute session which included: screening of global cognitive function (The Montreal Cognitive Assessment, MoCA; Nasreddine et al., 2005); the inhibition measure (Stroop Test; Stroop, 1935); the flexibility measure (Trail Making Test, TMT A and B; Reitan 1955); working memory measure (forward and backward Digit Span, WAIS III; Wechsler, 1981); several measures of ability to select a rule, maintain it, and switch to a new rule are from

Burgess and Shallice (1997), for the Brixton test and Nelson (1976), for the Wisconsin Card Sorting Test (WCST); and semantic fluency as represented by the total number of words produced in 2 min for the category Animals (Cardebat et al., 1990). Table 1 provides a detailed description of the raw cognitive measures as well as a statistical comparison of group means. Furthermore, the older adults' cognitive scores (not shown in **Table 1**) were within the average range according to all psychometric standardized data, suggesting normal cognitive functioning within the older adult group. All participants gave written informed consent to the protocol, which was approved by the Institut universitaire de gériatrie de Montréal Human Ethics Committee and by the Regroupement Neuroimagerie/Québec (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. Finally, in order to clearly identify subgroups of older participants according to their cognitive control profile, classification was based on their z-score for neuropsychological tests.

2.2 Characterization of Older Subgroups

Five executive z-scores for each older participant were entered into hierarchical cluster analysis with CLUSTAN (Aldenderfer and Blashfield, 1984). Using the Clustan Graphics program (version 5.27), case classification was based on the squared Euclidean distance as a coefficient of similarity, and on the Ward method of classification (Ward, 1963). The k-means clustering procedure of relocation was then applied to ensure that the two-cluster solution was stable. This procedure allowed for the identification of two possible natural older subgroups of participants, based on their performances on five executive measures (TMT B/A, digits backward, number of errors on the Brixton test, number of errors on the WCST, number of words produced correctly for the semantic fluency task). This grouping was confirmed *a posteriori* using an independent-samples t-test, which revealed that the two subgroups (henceforward referred to as the updating-profile and shifting-profile groups) differed significantly on five neuropsychological tests (**Table 2** and **Figure 1**).

The updating-profile group scored significantly higher on the backward digit span and Trail Making Test (Part B) than on the WCST, Brixton, and semantic fluency tests. Conversely, the shifting-profile group scored significantly higher on the WCST, Brixton, and semantic fluency tests than on the backward digit span and Trail Making Test (Part B). Thus, the latter group's executive performance relied more on their shifting ability than on updating/working memory, which the former group depended on more.

A cluster analysis approach was also performed on the group of younger participants. However, the results provided no clear indication of a given cognitive profile associated with a sub-group of participants. Thus, for younger participants, behavioural data were analysed as a group.

2.3 Experimental Procedure

The word-matching task used in this study was based on the computerized WCST developed and adapted to fMRI by Monchi et al. (2001) and Simard et al. (2011). The word-matching task was administered using stimulus presentation software (Media Control Function; Digivox, Montréal, Canada). Throughout the task, three reference cards based on three semantic rules were presented in a row at the bottom of the screen, displaying moderately, atypical, and functionally related words (see **Figure 2** for example). In each trial, a new target card was presented in the middle of the screen above the reference cards; it displayed a highly typical word. Participants must then match the target card with one of the reference cards based on moderately typical, atypical, or functional relatedness. Participants used a joystick to select among the three reference words, pressing left, right, or upward to select the reference word on the left, on the right, or in the middle, respectively (the description of selection stimuli is reported in **Supplementary Data Sheet 1**).

The word-matching task trials contained two periods: matching and feedback.

- The matching period started with the presentation of a new target card (highly typical word). The participant then chose one of the three reference words by using one of the three joystick directions. The length of each matching period depended on the participant's response times, which varied between 1470 and 4690 milli-seconds (ms) for this task. The period ended when the participant provided a selection response.
- The feedback period was indicated by a blue screen, which lasted for 500 ms and started as soon as a first correct match was made. Feedback was conveyed through a specific cue lasting for 2000 ms. An incorrect match was indicated by a red cross, whereas a correct match was indicated by a green check mark, which informed participants that the current matching rule was the correct one and that they should maintain the same rule as in the previous trial (see **Figure 2** for experimental procedure).
- In addition, there were control trials during which the target card was represented by a series of letters (e.g., AAAA), which was identical with one of the three reference cards (e.g., aaaa, bbbb, cccc). These trials involved pairing a target with an identical reference card (alphabetic association: AAAA with aaaa). No rule changes occurred in the control condition and control feedback indicated a correct or incorrect match.

All participants had one fMRI session, which consisted of four runs. Blocks of each of the four trials (the three semantic rule trials and the control trial) were presented in pseudo-random order four times per run. The rules changed without warning and the new correct rule would be applied and maintained until the participant achieved five to six consecutive correct matching trials (maintaining a rule if shown a green check mark) or had to switch it (if presented with a blue screen as feedback). It is worth mentioning that no participant reported learning the sequence regularity or having deduced the frequency of the changing rule. The control block consisted of eight trials. For each participant, the total number of trials per run changed according to performance, which depended on the number of errors. The participants were fully trained on the word-matching task by performing a block of conditions outside the scanner. Each participant needed to reach a performance level of 90% correct matching trials and have less than 5% of set-loss and perseverative errors before moving on to the scanning session.

The stimuli were presented via an LCD projector onto a mirror placed in front of the participant in the MRI scanner. Stimuli were outlined in black against a white background to improve visual contrast. All words were displayed horizontally at the top of the screen and were centred on a computer screen placed 50 cm away from the participant. The target word was placed in a larger rectangle and subtended a visual angle of 26.6° horizontally and 13.8° vertically. All words were presented in 28-point Arial font, and reference words were placed in three small rectangles 1.3 cm apart from each other.

For this study, we explored, exclusively, executive processing during the word-matching task. All correct (5–6) consecutive matching trials, after the maintenance feedback period and the correct trial after switch feedback, were taken into account for behavioural and imaging analysis, as were the correct control matching trials. To ensure that the rule was successfully acquired after rule-matching change (related to the search for a correct rule), we removed the first correct trial after switch feedback.

3 DATA ANALYSIS

3.1 Behavioral Data

Two behavioral measures were also collected: response times and correct responses (defined as 5 or 6 consecutive correct matching trials after maintenance and switch feedback). Intergroup analyses were performed using SPSS 18.0 software for Mac (IBM SPSS Statistics 18). A comparison ANOVA was done between the two groups (younger and older) for each executive component (henceforth, matching after maintenance feedback is referred to as *maintain rule* and matching after switch feedback as *switch rule*) and between these executive components for each group (younger and older). For these analyses, the response times for control matching trials were subtracted from those for matching trials after maintain rule in order to account for age-related decline in motor speed (Fristoe et al., 1997; Martins et al., 2014). In addition, errors were analysed for each group (younger vs. older) and a one-way ANOVA was carried out.

Results for response times and correct responses were divided into two parts; the first part (A) was based on a comparison between groups (younger vs. older), and the second part (B) was based on a comparison within the older group. This latter part of the study was exploratory.

3.2 fMRI Scanning

3.2.1 Image Acquisition

Participants were scanned at the Unité de Neuroimagerie Fonctionnelle of the Institut de Gériatrie de Montréal using a 3T Siemens Trio Magnetom MRI scanner (Siemens AG, Erlangen, Germany). The structural scan was a high-resolution T1-weighted 3D-MPRAGE, sagittal plane acquisition, field of view (FOV) = 256 mm, and matrix size = 256 x 256. In addition, we acquired functional images (T2* weighted, TR= 2500 ms, TE= 30 ms, 36 slices parallel to the anterior and posterior commissure (AC-PC) line, slice thickness = 3.5 mm with 3.5 mm^3 isotropic voxels, distance factor 0% (gap = 0 mm), Flip-angle = 90°, matrix = 64 x 64). Each 252-volume functional run lasted 10.30 min; four such runs were acquired for each participant. The stimulus presentation and the scanning were synchronized at the beginning of each run. To minimize head movement during scanning, cushions were placed between the subject's head and the coil.

3.2.2 fMRI Data Analysis

FEAT (FMRI Expert Analysis Tool) Version 5.98, part of the FSL analysis package (FMRIB's Software Library, Version 4.1.4[2]), was used to conduct image pre-processing procedures. We corrected for head motion using MCFLIRT (FMRIB's motion correction linear image registration tool; Jenkinson et al., 2002), and also used the fsl_motion_outliers script to detect and remove any volumes with excessive head motion. Non-brain tissue was removed using BET (Brain Extraction Tool; Smith, 2002). Grand-mean intensity normalization was applied to the 4D dataset from each run based on multiplicative scaling factor. We applied a Gaussian kernel of 6 mm FWHM for spatial smoothing, and for temporal filtering, a high-pass filter was applied to remove low-frequency noise using Gaussian-weighted least-squares straight-line fitting (1/60 Hz). Temporal auto-correlation was corrected by using pre-whitening as implemented by FILM (FMRIB's improved linear model). Functional images of each participant were co-registered to structural images in native space, and structural images were normalized to Montreal Neurological Institute (MNI) standard space using FSL's MNI Avg 152 T1 2 x 2 x 2 mm. The same transformation matrices used for structural-to-standard transformations were then used for functional-to-standard space transformations of co-registered functional images.

The FEAT module in FSL was used for first level analysis. An event-related design was used to model the fMRI data, allowing for inference based on contrast. We included five different event

---

[2] www.fmrib.ox.ac.uk/fsl

types in the design matrix: typical, functional, and atypical maintain rules; switch rules; and control trials. The maintain rule period was defined on the basis of the time period, for which each length varied between trials depending on the participant's response time. This period started with the presentation of a new trial and ended only when the participant provided a selection response. The maintain rule period was convolved with a double-gamma hemodynamic response function (HRF). The switch rule period was defined as a shift event based on the second correct trial after switch feedback, during which the participant had to discover and apply the new matching rule, convolved with a double-gamma HRF. The aim was to separate correct maintain and switch-rule periods as well as control trials. Motion regressors generated by MCFLIRT were then included as confound covariates. A first-level GLM analysis was carried out separately for each run, followed by a second-level fixed-effects analysis. We then combined these analyses across all participants in group-level analysis (Higher-level) using a mixed effects analysis controlling for variation within and between participant groups, using FLAME (FMRIB's Local Analysis of Mixed Effects). For age-group comparison (younger vs. older), statistical results were at a threshold voxel significance level of $Z > 2.3$, and a whole-brain-corrected cluster significance threshold of $p < 0.05$. To explore the effect of cognitive control profile on activation changes in the older group, an exploratory study was conducted. For the older subgroup's exploratory study, all the steps in the analysis were as described above. However, Flame 1 and 2 were added at a higher level of analysis due to the small sample size of the older subgroups. For the same reason, the statistical results were at a threshold voxel significance level of $Z > 1.96$ and a whole-brain-corrected cluster significance threshold of $p < 0.05$ for the main-effect of each subgroup. For subgroup difference analysis, due to a limited sample size, a more liberal threshold at $p < 0.001$ was set. In this manner, a literature-guided hypothesis was tested for activity differences specifically located in frontoparietal regions, while ensuring that no other significant clusters were found in the brain.

To investigate regional differences of BOLD (blood-oxygen-level dependent) signal changes in the areas that showed significant activation, we used a region of interest (ROI) approach. Each ROI centered on a peak level of significant activation produced by a group average of the statistical maps. For the between-group comparison (younger vs. older), these ROIs were in the right posterior prefrontal cortex [BA 6/8/44; x = 37; y = 18; z = 52] and in the left inferior parietal cortex [BA 39/40; x = –33; y = –61; z = 39]. For between older subgroups (updating-profile vs. shifting-profile): within the left dorsolateral prefrontal cortex [BA 9/46; x = –42; y = 10; z = 35] and the left inferior parietal cortex [BA 39/40; x = –33; y = –61; z = 39] were considered as ROIs. These ROIs (identified in our participants) have been widely reported in cognitive control tasks in previous studies (Rypma et al., 2006; Badre and D'Esposito, 2007; Nagel et al., 2008; Niendam et al., 2012; Whitney et al., 2012; Noonan et al., 2013). ROI masks were generated with a 4 mm-radius sphere centered on the peak voxel coordinate within each significant cluster. The mean BOLD signal change of the ROIs was extracted separately for each participant from the maintain rule and switch rule. Finally, we conducted a correlation analysis for each age group and also for each older subgroup to investigate potential patterns of relation between behavioral performance (response times, correct responses) and BOLD signal changes during the word-matching task. Additionally, the Fisher r-to-z transformation was also applied to calculate a value of z that can be applied to assess the significance of the difference between two correlation coefficients found, in one case, between younger and older groups and, in the other, older subgroups separated by cognitive profile.

4 RESULTS

4.1 Part A: Age-Related Neurofunctional Reorganization

4.1.1 Behavioral Performance

Response times in maintain rule proved to be significantly longer in the older adult group than in the younger group [M_{older} = 2741 ms, SD = 481; $M_{younger}$ = 2265 ms, SD = 705; F(1.38) = 6.219, p = 0.017]. The same was true in the switch rule [M_{older} = 2974 ms, SD = 793; $M_{younger}$ = 2365 ms, SD = 965; F(1.38) = 4.74, p = 0.036] and control condition [M_{older} = 1330 ms, SD = 166; $M_{younger}$ = 1048 ms, SD = 207; F(1.38) = 22.44, p = 0.001]. For the maintain rule condition, when control response times were taken into account, older adults showed no significant difference in response times compared to younger adults [F(1.38) = 1.704, p = 0.20] (**Table 3**). A 2 x 2 ANOVA was performed to explore the effects of age group (younger vs. older) and executive component (maintain rule vs. switch rule) on response times. There was a marginal effect of age group [F(1.38) = 3.64, p = 0.064], with response times slower in the older adults than in the younger adults. The interaction between age and executive component was also significant [F(2.38) = 7.32, p = 0.010]. The main effect analysis revealed a significant effect of the executive component [F(1.38) = 313.25, p = 0.001], showing that maintain rule took less time than switch rule. More specifically, for the maintain rule, planned comparisons did not reveal any significant effect of age [M_{older} = 1411 ms, SD = 383; $M_{younger}$ = 1217 ms, SD = 542; F(1.38) = 1.704, p = 0.20], whereas the older adults showed significantly longer response times in the switch rule condition than the younger adults. It is worth noting that there was no difference between older and younger participants in total correct responses or in the word-matching task [F(1.38) = 0.693, p = 0.41] regardless of feedback type, indicating that both younger and older adults performed well.

4.1.2 Imaging Results

The aim of this study was to investigate the impact of age on neuroimaging patterns during a word-matching task. The brain activation pattern was described for maintain rule and switch feedback compared to the control condition. Given the relevance of executive aspects in the word-matching task used in this study, we combined the three semantic relationships. We compared the average BOLD signal obtained during maintain rule and switch rule with the control matching condition. Intergroup analyses were also performed.

4.1.2.1 Maintain rule vs. control matching

As predicted, neuroimaging analyses revealed the involvement of cognitive control networks during the word-matching task in both groups (younger and older). The younger group showed significant activation in the right dorsolateral prefrontal cortex (BA 9/46), the left ventrolateral prefrontal cortex (BA 44/45), the bilateral insula (BA 41), the left lateral premotor cortex (BA 6), the left posterior prefrontal cortex (junction of BAs 6, 8 and 44), the bilateral superior parietal cortex (BA 7), and the left inferior parietal cortex (BA 39).

The older adults showed significant activation in the left ventrolateral prefrontal cortex (BA 44/45), the bilateral insula (BA 41), the bilateral posterior prefrontal cortex (junction of BAs 6, 8 and 44), the dorsolateral prefrontal cortex (BA 9/46) bilaterally, the left lateral premotor cortex (BA 6), the left inferior temporal cortex (BAs 37 and 20), the bilateral superior parietal cortex (BA 7), the left inferior parietal cortex (BA 39), the left occipital cortex (BA 18), and the right cerebellum.

The comparison between groups showed significantly greater activation in the older adults than in the younger ones in the left and the right hemispheres in the posterior cingulate cortex (BA 31), the right inferior temporal cortex (BA 37), the left inferior cortex (BA 40), the cerebellum bilaterally, the right occipital cortex (BA 18), and in the bilateral caudate nucleus. Comparison of younger minus older adults showed no significant difference (**Table 4** and **Figure 3A**; for younger and older see **Supplementary Table S1**).

4.1.2.2 Switch rule vs. control matching

As predicted, stronger activation was found in both groups in the switch rule relative to control matching (**Table 5**). The younger group showed significant activation in the right dorsolateral prefrontal cortex (BA 9/46), the left supplementary motor area (BA 6), the left ventrolateral prefrontal cortex (BA 44/45), the right posterior prefrontal cortex (junction of BAs 6, 8 and 44), the right anterior cingulate cortex (BA 32), the bilateral superior parietal cortex (BA 7), the inferior parietal cortex bilaterally (BA 39), the left occipital cortex (BA 18), and the bilateral caudate nucleus.

The older adults showed significant bilateral activation in the frontopolar cortex (BA 10), the right dorsolateral prefrontal cortex (BA 9/46), the left supplementary motor area (BA 6), bilateral insula (BA 41), the left posterior prefrontal cortex (junction of BAs 6, 8 and 44), the bilateral lateral prefrontal cortex (BA 6), the inferior parietal cortex bilaterally (BA 40), and the right superior parietal cortex (BA 7).

The comparison between groups showed significantly greater activation in the older adults than in the younger adults in the left supplementary motor area (BA 6), the left inferior parietal cortex (BA 39/40), and the right cerebellum. Comparison of younger minus older adults showed no significant difference (**Table 5** and **Figure 3B**; for younger and older see **Supplementary Table S2**).

4.1.2.3 Switch rule vs. maintain rule

When the switch rule was compared with the maintain rule, the younger group showed significant activation in the left frontopolar cortex (BA 10), the left anterior cingulate (BA 32), the right dorsolateral prefrontal cortex (BA 9/46), the right posterior prefrontal cortex (junction of BAs 6, 8 and 44), the right inferior parietal cortex (BA 40), the bilateral superior parietal cortex (BA 7), and the left occipital cortex (BA 18).

The older adults showed significant activation in the left frontopolar cortex (BA 10), the left dorsolateral prefrontal cortex (BA 9/46), the left supplementary motor area (BA 6), the left inferior parietal cortex (BA 40), the superior parietal cortex bilaterally (BA 7), and the left occipital cortex (BA 18).

The comparison between groups showed significantly more activation in the older adults than in the younger adults in the left posterior cingulate cortex (BA 31), the left inferior parietal cortex (BA 39), the superior parietal cortex (BA 7), and the left occipital cortex (BAs 18 and 19). The comparison of younger minus older adults showed significantly more activation in the right supplementary motor cortex (BA 6) and the right posterior prefrontal cortex (junction of BAs 6, 8, and 44) in the younger adults (**Table 6** and **Figure 4A**; for younger and older see **Supplementary Table S3**).

The comparison of brain activity patterns in the two age groups revealed more pronounced activity in the left inferior parietal cortex for the older adults and in the right posterior prefrontal cortex for the younger adults only when the maintain rule was subtracted from the switch rule. To explore the age-related neurofunctional relevance of these regions involved in the executive processes underlying the word-matching task, we first tested for an interaction effect before exploring the simple effects. Finally, we did a correlation analysis between older and younger participants' performance and brain activity within these regions.

4.1.2.4 ROI BOLD signal and performance in older and younger groups

The results of 2 (group) x 2 (executive component) mixed effects ANOVA on BOLD signal in the left inferior parietal cortex revealed a significant main-effect of group [F(1.38) = 5.923, p = 0.020] and executive component [F(1.38) = 32.72, p = 0.001], but no group x executive component interaction [F(2.38) = 0.478, p = 0.49]. However, planned comparison showed significant differences between younger and older adults. The BOLD signal change in the left inferior parietal cortex was significantly greater for older adults when compared to younger adults only for switch rule [F(1.38)= 62.88, p = 0.001]. No significant main-effect of group [F(1.38) = 2.169, p = 0.149] or executive component [F(1.38) = 0.389, p = 0.537] was observed in the right posterior prefrontal cortex, with no group x executive component interaction [F(2.38) = 3.140, p = 0.073].

Pearson's correlation analysis conducted between behavioral performance (response times, correct responses) and BOLD signal changes in the left inferior parietal cortex [BA 39/40; x = –33; y = –61; z = 39] for younger and older adults (**Figure 4B**) showed significant negative correlation with response times (r = –.72; p = 0.001) and significant positive correlation with correct responses (r = .55; p = 0.011) in the older group. However, the younger adults showed no significant correlation with response times (r = .098; p = 0.68) or correct responses (r = –.077; p = .74). The difference in correlation coefficients between the BOLD signal changes in the left inferior parietal cortex and the response times was statistically significant (z = -2.94; p = 0.0003) between the two groups (younger vs. older), as well as for the correct responses (z = 2.03; p = 0.042). There was no significant correlation between BOLD signal changes in the right posterior prefrontal cortex [BA 6/8/44; x = 37; y = 18; z = 52] and behavioral performance for younger (response times: r = .028; p = 0.90; correct responses: r = .04; p = 0.85) and older adults (response times: r = -.43; p = 0.06; correct responses: r = .19; p = 0.40) (not shown in **Figure**

4B). The statistical difference between the two correlation coefficients for the two groups (younger vs. older) was not significant for response times (z = 1.42; p = 0.15) or for correct responses (z = -0.44; p = 0.65).

4.2 Part B: Cognitive Control Profiles and Neurofunctional Reorganization in Older Adults

4.2.1 Behavioral Performance

The two older subgroups' behavioral performance (correct responses and response times) on the word-matching task was equivalent (**Table 7**). A comparison between the two older subgroups (updating-profile vs. shifting-profile) for maintain rule and switch rule was performed using an independent-group t-test. The difference between the two older subgroups was not significant for maintain rule [t(18) = -.641, p = 0.52] or for switch rule [t(18) = -.440, p = 0.66].

4.2.2 Imaging Results

4.2.2.1 *Maintain rule vs. control matching*

The updating-profile group showed significant activation in the left ventrolateral prefrontal cortex (BA 47/12), left dorsolateral prefrontal cortex (BA 9/46), the left posterior prefrontal cortex (junction of BAs 6, 8, and 44), the left lateral premotor cortex (BA 6), and the cerebellum bilaterally. The shifting-profile group showed significant activation in the left inferior parietal cortex (BA 40), the left superior parietal cortex (BA 7), and the left inferior temporal cortex (BA 20). The comparison between the two groups showed more activation in the updating-profile group than in the shifting-profile group within the left dorsolateral prefrontal cortex (BA 9/46). The reverse inter-group comparison showed no significant difference (**Table 8** and **Figure 5A**; for each older subgroups see **Supplementary Table S4**).

4.2.2.2 Switch rule vs. control matching

The updating-profile group showed significant activation in the right dorsolateral prefrontal cortex (BA 9/46), the left posterior prefrontal cortex (junction of BAs 6, 8, and 44), the right lateral premotor cortex (BA 6), the left superior parietal cortex (BA 7), the occipital cortex (BAs 18 and 19), and the cerebellum bilaterally. The shifting-profile group showed significant activation in the left frontopolar cortex (BA 10), the bilateral posterior prefrontal cortex (junction of BAs 6, 8, and 44), the right dorsolateral prefrontal cortex (BA 9/46), the left ventrolateral prefrontal cortex (BA 44/45), the right lateral premotor cortex (BA 6), the right superior parietal cortex (BA 7), the left inferior parietal cortex (BA 39/40), and the right cerebellum (**Table 9** and **Figure 6A**; for each older subgroup see **Supplementary Table S5**). The comparison between the two subgroups showed more activation in the shifting-profile group than the updating-profile group within the left inferior parietal cortex (BA 39/40). The reverse inter-group comparison showed no significant difference.

The comparison of brain activity patterns of the two older subgroups revealed more pronounced activity in the left dorsolateral prefrontal cortex for the updating-profile group, only during maintain rule. However, the shifting-profile group showed more pronounced activity in the left inferior parietal cortex (BA 39/40), only during switch rule. To explore the functional changes and age-related differences in cognitive control profiles, an interaction effect was tested before exploring simple effects. Finally, a correlation analysis was performed between the updating-profile group and the shifting-profile group's behavioral performance and BOLD signal, within functionally relevant regions.

4.2.2.3 ROI BOLD signal and performance in the two older subgroups

The results of 2 (cognitive profiles) x 2 (executive component) mixed effects ANOVA on BOLD signal in the left dorsolateral prefrontal cortex revealed a significant main-effect of cognitive profile [F(1.18) = 4.41, p = 0.051] and executive component [F(1.18) = 9.129, p = 0.008], but no cognitive profile x executive component interaction [F(2.18) = 0.172, p = 0.68]. Similarly, significant main-effects of cognitive profile [F(1.18) = 6.151 , p = 0.023] and executive component [F(1.18) = 25.48, p = 0.001] were observed in the left inferior parietal cortex in the absence of a cognitive profile x executive component interaction [F(2.18) = 1.27; p = 0.275]. However, planned comparison of BOLD signal change in the left dorsolateral prefrontal cortex showed significant difference between updating-profile and shifting-profile. The BOLD signal change in the left dorsolateral prefrontal cortex was significantly greater for the updating-profile when compared to the shifting-profile, only for the maintain rule (p = 0.028). Conversely, the BOLD signal changes in the left inferior parietal cortex were significantly greater for the shifting-profile when compared to the updating-profile, only for the switch rule (p = 0.038).

Spearman’s correlation analysis was conducted between behavioral performance (response times, correct responses) and BOLD signal changes in the left dorsolateral prefrontal cortex [BA 9/46; x = -42; y = 10; z = 35] and in the left inferior parietal cortex [BA 39/40; x = –33; y = –61; z = 39] for both older subgroups (updating-profile and shifting-profile).

During maintain rule, relative to control matching (**Figure 5B**), the correlation between BOLD signal changes in the left dorsolateral prefrontal cortex and correct responses was significantly positive for the updating-profile group (r = .83, p = 0.005), while for the shifting-profile group there was no significant correlation (r = –.25, p = 0.486). The difference in correlation coefficients between BOLD signal changes in the left dorsolateral prefrontal cortex and correct responses was significant (z = 2.63; p = 0.008) between updating-profile and shifting-profile groups. Furthermore, there was no significant correlation between the BOLD signal change in the left dorsolateral prefrontal cortex and response times in either of the two older subgroups (updating-profile: r = –.50, p = 0.055; shifting-profile: r = .60, p = 0.085). The difference between correlation coefficients was significant for updating-profile and shifting-profile groups (z = -2.18; p = 0.002).

Comparing switch rule to control matching (**Figure 6B**), there was no correlation between BOLD signal changes in the left inferior parietal cortex and correct responses (r = –.14, p = 0.736) for the updating-profile, while positive correlation was observed for the shifting-profile group (r = .82, p = 0.002). Note: one outlier participant from the updating-profile group (extremely long response time) was removed from correlation analysis. The difference between the two correlation coefficients was significant for updating-profile and shifting-profile groups (z = -2.28; p = 0.022).

Furthermore, there was no correlation between the BOLD signal change in the left inferior parietal cortex and response times (r = –.48, p = 0.22) for the updating-profile group, while a negative correlation was observed for the shifting-profile group (r = –.72, p = 0.023). The difference between the two correlation coefficients was not significant for the updating-profile or the shifting-profile groups (z = 0.71; p = 0.47).

5 DISCUSSION

The aim of this study was to explore the age-related, neurofunctional basis for executive semantic processing of words. It is known that healthy aging is associated with neurofunctional reorganization that maintains cognitive performance. Herein, this investigation evaluated the effects of healthy aging and cognitive changes on executive function, neurofunctional activation, and behavioral measures during a word-matching task. To do so, a new word-matching task was employed that was based on the WCST and was adapted for fMRI by Monchi et al. (2001) and Simard et al., (2011). Results demonstrated that the shift in age-related brain activation from frontal to parietal regions is another form of neurofunctional reorganization, which sustains executive processes during a word-matching task. In addition, differences in cognitive control profile during aging appeared to be mediated by specific neurofunctional reorganization, which maintains task performance. Taken together, these results demonstrate functional changes during a word-matching task related to age and cognitive control profile. Further, correlations were identified between behavioral task performance and changes in brain activity within the relevant frontoparietal regions. These findings are discussed below.

5.1 Age-Related Neurofunctional Reorganization

As predicted, and consistent with the literature (Jefferies and Lambon-Ralph, 2006; Noonan et al., 2013; Whitney et al., 2011), the cognitive control network was found to be involved in executive aspects of semantic processing, including the lateral prefrontal cortex, the anterior cingulate cortex, the parietal and temporal cortices, which are responsible for executive processing in the semantic domain that overlaps general executive processing. These findings are consistent with the recent neurobiology of language model, which proposes that successful language processing is based on the interaction between the neural mechanisms underlying cognitive control and the semantic system (Badre et al., 2005; Nagel et al., 2008). The brain activity patterns that emerged during the word-matching task revealed some age-related changes that appear to support better performance, even though the response time of older adults (compared to younger adults) was significantly longer after switch than maintenance feedback. It should be noted that differences in age-related response times were not systematically observed when control-matching performance was taken into account through a motor-speed measure. There was an age-related decline in performance of complex executive tasks such as the WCST, but controlling for a decrease in perceptual-motor speed in a task involving perception of stimuli followed by a simple motor response – the control condition (i.e., alphabet pairing in our study) – significantly reduced this performance decline (Fristoe et al., 1997; Martins et al., 2014). Taken together, our findings along with evidence from cognitive aging studies suggest that age-related differences in the reliance on high-level executive control processes, as it related to switching process (i.e. switch rule) during a word-matching task, may undergo greater age-related neurofunctional changes than the maintenance processes (i.e. maintain rule).

Regarding the maintain rule, bilateral frontal activation (**Table 4**) observed in older adults, compared to more lateralized activations in younger adults, suggests that the posterior prefrontal cortex (junction of BAs 6, 8, and 44) and the dorsolateral prefrontal cortex (BA 9/46) were recruited more when older participants maintained and updated rule classifications in working memory. The presence of posterior prefrontal involvement during different cognitive control tasks has been attributed to flexible cognitive performance (Brass and Von Cramon, 2004; Derrfuss et al., 2005). However, regarding these neurofunctional patterns, the differential involvement of the two lateral prefrontal regions (dorsal and ventral parts) in cognitive control may mediate different kinds of control. Indeed, Spreng et al., (2010) have suggested that older adults show reduced maintenance of information mediated by the left ventrolateral prefrontal cortex when compared to greater activation in the dorsolateral prefrontal cortex, which is more involved in strategic control.

When older adults were compared with younger ones, activations were noted in the posterior cingulate cortex, inferior parietal cortex, inferior temporal cortex, occipital cortex, and the superior and inferior portions of the cerebellum. Such activations are consistent with the pattern of activity seen during a set of semantic tasks, thought to require activation of specific conceptual knowledge features (Cristescu et al., 2006). The activations reported in the cerebellum are compatible with studies that have shown such activation in cases where high-level language processing is required in the context of tasks that require frontal areas to support lexico-semantic strategies (Walter and Joanette, 2007; Murdoch, 2010), as well as the storing and maintenance of information in working memory (Bellebaum and Daum, 2007). Overall, these changes in neurofunctional patterns support the hypothesis that older adults rely more on posterior regions in order to efficiently process semantic rules during word matching. The more demands are placed on their semantic knowledge, the more their strategic semantic processes involve the posterior regions, that underlie successful cognitive performance (Hazlett et al., 1998; Wieranga et al., 2008; Ansado et al., 2013b; Lacombe et al., 2015).

As predicted, switch rule compared to control matching was associated with bilateral frontal and parietal activations in both younger and older adults, although activation was greater in older adults (**Figure 3B**). These regions have been found to be consistently related to cognitive switching within a WCST paradigm (Monchi et al., 2001; Simard et al., 2011). Greater activity was displayed in cognitive-control-related frontoparietal regions that support higher-level executive processing. However, these networks may be differentially engaged during executive tasks (Braver et al., 2009). To improve cognitive performance, the brain activation pattern in older adults showed involvement of the frontopolar cortex and insula, possibly recruited to support processing task demands thought to be sub-served by primary neural resources.

Increased frontal activation during word-matching confirms the frontal cortex's contribution to semantic retrieval, selection, and control demands. It remains to be determined whether semantic executive functions are primarily sustained by the frontal cortex or by other regions. Within cognitive control networks, frontoparietal regions may be differentially engaged depending on executive control demands. For example, maintaining information over a period of time and selecting responses have been associated with more frontal than parietal engagement (Braver et al., 2003). Furthermore, the parietal regions seem to represent a convergence zone for many executive domains (Duncan, 2006). Many neuroimaging studies have emphasized the parietal cortex's contribution to a wide range of tasks, including working memory (Derrfuss et al., 2005; Riis et al., 2008) and interference resolution (Campbell et al., 2012; Zysset et al., 2007). Conceivably, involvement of parietal regions may mechanistically underlie task performance maintenance in healthy aging.

The most relevant neural pattern was observed for intergroup comparisons when maintain rule was subtracted from switch rule (**Figure 4A**). Indeed, older adults recruited the inferior parietal region (BA 39/40), while younger adults recruited the posterior prefrontal region (junction of BAs 6, 8 and 44). This age-related shift in activation from anterior (frontal) to posterior (parietal) region reflects different patterns of activation in the two age groups, indicating the use of different brain networks to mediate task performance. An integrative theory of aging proposed by Park and Reuter-Lorenz (2009) suggests that a dynamic-adaptive, neurofunctional reorganization takes place in which the older brain builds neural scaffolds to engage more functional resources and to compensate for the insufficiency of available basic-neural resources. Based on the results of this study, older adults tend to recruit parietal regions as an alternate strategy to ensure successful behavioral performance avoiding limited frontal resources. Furthermore, in older adults activity in the left inferior parietal region increased with a correct response and with a decreased response speed, whereas younger adults showed an inverse behavioral pattern (**Figure 4B**). This region-dependent pattern of activation and performance suggests that involvement of the inferior parietal region is necessary for older adults as another form of neurofunctional reorganization to maintain processing efficiency during a word-matching task.

In this context, activation in parietal regions can be considered as a more straightforward form of older-brain neural scaffold in response to neural insult and to age-related changes in frontal regions (Reuter-Lorenz and Cappell 2008; Peelle et al., 2013). According to recent studies (Harding et al., 2015; Grady et al., 2016), the age-related changes in functional connectivity between frontal and parietal nodes are relevant in task performance, since greater neural recruitment in this cognitive control network co-occurs with greater improvements in executive processing. Those studies described patterns reflecting the neurofunctional adaptability of neural resources in healthy aging within the frontoparietal network, with a decrease in age-related parietal structural changes. This suggests that one of many mediating factors for neural resource reallocation is a cognitive control ability that enhances the development of dynamic neuro-functional reorganization trajectories that compensate for changes in the aging brain (Reuter-Lorenz and Cappell, 2008). These results provide some evidence for the HAROLD phenomenon in parietal regions (Cabeza, 2002; Grady et al., 2002; Angel et al., 2010). More interestingly, despite a decline in cognitive control processing in healthy aging, increasing reliance on parietal regions may be a means by which to functionally and cognitively cope with limited frontal resources. This possibility is supported by a recent observation that the aging brain is widely involved in executive control of resources during highly process-dependent tasks (Bouaazaoui et al., 2014). Nevertheless, the lack of correlation between behavioral performance and the right posterior prefrontal cortex implies that this region is less critical to successful executive processing in semantic tasks than is the inferior parietal region, which is associated with executive semantic processing (Noonan et al., 2013; Peelle et al., 2013).

In summary, executive functions have been found to support semantic performance, with increased reliance on neural substrates that sustain the demand for higher executive control; these substrates include the inferior parietal region, which is correlated with age-related performance maintenance in older age. However, it seems reasonable that changes in executive functional organization in healthy aging underlie very different executive abilities, and by extension, might predict distinct cognitive profiles preferentially sustained by distinct neural substrates as suggested by Hull et al., (2008). This may also explain why inter-individual variability in executive performance is more evident among older adults than younger ones (Logan et al., 2002; Braver and West, 2008). These possibilities are explored in the next section.

5.2 Cognitive Control Profiles and Neurofunctional Reorganization in Older Adults

A common finding on cognitive aging is that changes in cognitive function tend to be accompanied by changes in cognitive control processes in healthy elderly adults (Braver et al., 2001; Velanova et al., 2007; Mudar et al., 2015). Age-related executive function is supported by at least two executive components (updating and shifting), which make different contributions to task performance and probably depend on different neural patterns in healthy aging. The existence of different components within executive function (updating and shifting) indicates that executive functioning is organized in a non-unitary, multifaceted way in normal aging – and throughout the lifespan (Hull et al., 2008).

In accordance with our second prediction, we found two subgroups of older adults (updating-profile and shifting-profile) who showed different neurofunctional patterns depending on their executive abilities while performing equally well on the word-matching task (response times and correct responses). According to the flexible hub theory (Cole et al., 2013), a cognitive control network including the lateral prefrontal cortex, posterior parietal cortex and insula (which is known as the frontoparietal network) supports functional adaptation changes in healthy aging. Moreover, data supporting the theory indicates that age-related neurofunctional ability consists in flexibly coordinating cooperation between the cognitive control and language regions, to maintain task performance. Regarding the relevant functional regions and age-related executive changes, the findings reported herein support the hypothesis that older adults have developed a cognitive style that makes greater use of neural resources that mediate cognitive control of task performance.

Furthermore, several prior studies have highlighted activity changes in the frontoparietal network based on inter-individual differences in task performance. For example, Rypma et al., (2002) analyzed specific ROIs (dorsolateral, ventrolateral, posterior prefrontal cortex, and parietal cortex) and found that the frontoparietal network was associated with maintenance performance. In that study, older participants with slow response times showed bilateral activation in the dorsolateral prefrontal cortex, whereas older participants who responded faster showed widespread bilateral parietal cortex activation. Moreover, Gevin and Smith (2000) found differences in the involvement of frontal and parietal regions based on their participants' cognitive ability. In their study, older adults with higher verbal ability showed greater activation in parietal regions, while those with lower verbal ability exhibited more activation in frontal regions.

These findings suggest that individual differences in performance may be due to distinct functional changes. In the same vein, Peelle et al. (2013) found differences in the involvement of frontal and parietal regions depending on older participants' cognitive ability. They reported that older adults with higher cognitive function showed greater activation in parietal regions, while those with lower function exhibited more activation in frontal regions. These group differences suggest that older participants with more cognitive resources are able to adopt a strategy that involves larger, more distributed brain areas, while those with fewer resources use a strategy based on specific frontal regions.

Similarly, our results support this assumption since different patterns of neurofunctional reorganization in the frontoparietal network were found to relate to the elderly participant's cognitive control profile. The updating-profile group improved their behavioral performance during maintain rule with more reliance on the dorsolateral prefrontal region (Figure 5B), which the shifting-profile group did not. Conversely, the inferior parietal region was more relevant for successful performance in the shifting-profile participants than for the updating-profile group's performance during switch rule (Figure 6B). This result is of considerable importance, since it provides evidence for changes in executive process organization in healthy aging. As proposed by Noonan et al., (2013), the executive control over semantic processing underlies a flexible neural network including the bilateral posterior prefrontal cortex and the left inferior parietal cortex. Disruption of one region results in shift activation in other parts of the network. Hence, a healthy aging brain recruits more than one pathway to preserve cognitive performance.

6. CONCLUSION

Age-differences in fronto-parietal region involvement during executive processing in a word-matching task are associated with behavioral performance maintenance by recruiting the inferior parietal region when executive frontal resources are in high demand. This greater reliance on the inferior parietal region by older adults could be interpreted as a neurofunctional change reflecting age-associated mechanistic differences in the executive control system, which are known to be dynamic in healthy aging.

A distinction between frontal and parietal regions was also observed in older adults, which was related to cognitive control profile. This finding appears to be consistent with changes in executive process organization in healthy aging as proposed by Hull et al., (2008) and Adrover-Roig and Barceló (2010). Thus, diversity in executive control system serves to adapt older brain to different functional changes. This characterizes older people in terms of frontal and parietal network utilization for more proficient executive semantic processing, as assessed by a word-matching task. The relationships between changes in brain activity and in executive ability in healthy aging are relevant to future cognitive aging studies and more specifically to brain-injured individuals with semantic aphasia as well as executive dysfunction. We acknowledge that the relatively small number of elderly participants included in our second study represents a limitation; the study should be replicated with a larger sample. Even so, as discussed, our findings are in accordance with various previous studies.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Thomas Espeseth for his relevant critical revision of this manuscript.

References

Adrover-Roig, D., and Barceló, F. (2010). Individual differences in aging and cognitive control modulate the neural indexes of context updating and maintenance during task switching. *Cortex.* 46, 434–50. doi:10.1016/j.cortex.2009.09.012.

Adrover-Roig, D., Sesé, A., Barceló, F., and Palmer, A. (2012). A latent variable approach to executive control in healthy ageing. *Brain Cogn.* 78, 284–99. doi:10.1016/j.bandc.2012.01.005.

Aldenderfer, M. S., and Blashfield, R. K. (1984). Cluster analysis. *Beverley Hills*: Sage

Angel, L., Fay, S., Bouazzaoui, B., and Isingrini, M. (2010). Individual differences in executive functioning modulate age effects on the ERP correlates of retrieval success. *Neuropsychologia* 48, 3540–3553. doi:10.1016/j.neuropsychologia.2010.08.003.

Ansado, J., Monchi, O., Ennabil, N., Deslauriers, J., Jubault, T., Faure, S., and Joanette, Y. (2013a). Coping with task demand in aging using neural compensation and neural reserve triggers primarily intra-hemispheric-based neurofunctional reorganization. *Neurosci. Res.* 75, 295–304. doi:10.1016/j.neures.2013.01.012.

Ansado, J., Marsolais, Y., Methqal, I., Alary, F., and Joanette, Y. (2013b). The adaptive aging brain: Evidence from the preservation of communication abilities with age. *Eur. J. Neurosci.* 37, 1887–1895. doi:10.1111/ejn.12252.

Badre, D., Poldrack, R. A., Paré-Blagoev, E. J., Insler, R. Z., and Wagner, A. D. (2005). Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. *Neuron* 47, 907–918. doi:10.1016/j.neuron.2005.07.023.

Badre, D., and D'Esposito, M. (2007). Functional magnetic resonance imaging evidence for a hierarchical organization of the prefrontal cortex. *J. Cogn. Neurosci.* 19, 2082–2099. doi:10.1162/jocn.2007.91201.

Badre, D., and Wagner, A. D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia* 45, 2883–901. doi:10.1016/j.neuropsychologia.2007.06.015.

Bellebaum, C., and Daum, I. (2007). Cerebellar involvement in executive control. *Cerebellum* 6, 184–192. doi:10.1080/14734220601169707.

Binder, J. R., Desai, R. H., Graves, W. W., and Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb. Cortex* 19, 2767–96. doi:10.1093/cercor/bhp055.

Binder, J. R., and Desai, R. H. (2011). The neurobiology of semantic memory. *Trends Cogn. Sci.* 15, 527–536. doi:10.1016/j.tics.2011.10.001.

Bookheimer, S. (2002). Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. *Annu. Rev. Neurosci.* 25, 151–88. doi:10.1146/annurev.neuro.25.112701.142946.

Bouazzaoui, B., Angel, L., Fay, S., Taconnat, L., Charlotte, F., and Isingrini, M. (2014). Does the greater involvement of executive control in memory with age act as a compensatory mechanism? *Can. J. Exp. Psychol.* 68, 59–66. doi:10.1037/cep0000005.

Brass, M., and Von Cramon, D. Y. (2004). Decomposing components of task preparation with functional magnetic resonance imaging. *J. Cogn. Neurosci.* 16, 609–620. doi:10.1162/089892904323057335 [doi].

Braver, T. S., Barch, D. M., Keys, B. A., Carter, C. S., Cohen, J. D., Kaye, J. A., Janowsky, J. S., Taylor, S. F., Yesavage, J. A., Mumenthaler, M. S., et al. (2001). Context processing in older adults: evidence for a theory relating cognitive control to neurobiology in healthy aging. *J Exp Psychol Gen* 130, 746–763. doi:10.1037/0096-3445.130.4.746.

Braver, T. S., Braver, T. S., Reynolds, J. R., Reynolds, J. R., Donaldson, D. I., and Donaldson, D. I. (2003). Neural mechanisms of transient and sustained cognitive control during task switching. *Neuron* 39, 713–726. doi:10.1016/S0896-6273(03)00466-5.

Braver, T. S., and West, R. (2008). Working memory, executive control and aging. *Handb. Aging Cogn.*, 311–372.

Braver, T. S., Paxton, J. L., Locke, H. S., and Barch, D. M. (2009). Flexible neural mechanisms of cognitive control within human prefrontal cortex. *Proc. Natl. Acad. Sci. U. S. A.* 106, 7351–6. doi:10.1073/pnas.0808187106.

Burgess, P.W. and Shallice, T. The Hayling and Brixton Tests. Bury St.Edmunds, UK: Thames Valley Test Company, 1997.

Burke, D. M., and Shafto, M. A. (2004). Aging and language production. *Curr. Dir. Psychol. Sci.* 13, 21–24. doi:10.1111/j.0963-7214.2004.01301006.x.

Cabeza, R. (2002). Hemispheric Asymmetry Reduction in Older Adults : The HAROLD Model. *Psychol. Aging* 17, 85–100. doi:10.1037//0882-7974.17.1.85.

Campbell, K. L., Grady, C. L., Ng, C., and Hasher, L. (2012). Age differences in the frontoparietal cognitive control network: Implications for distractibility. *Neuropsychologia* 50, 2212–2223. doi:10.1016/j.neuropsychologia.2012.05.025.

Cardebat, D., Doyon, B., Puel, M., Goulet, P., & Joanette, Y. (1990). Formal and semantic lexical evocation in normal subjects. Performance and dynamics of production as a function of sex, age and educational level. Acta Neurologica Belgica, 90(4), 207–217. doi: PMID 2124031.

Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., and Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. *Nat. Neurosci.* 16, 1348–1355. doi:10.1038/nn.3470.

Collette, F., Hogge, M., Salmon, E., and Van der Linden, M. (2006). Exploration of the neural substrates of executive functioning by functional neuroimaging. *Neuroscience* 139, 209–21. doi:10.1016/j.neuroscience.2005.05.035.

Collette, F., and Salmon, E. (2014). Les modifications du fonctionnement exécutif dans le vieillissement normal. *Psychol. Fr.* 59, 41–58. doi:10.1016/j.psfr.2013.03.006.

Cristescu, T. C., Devlin, J. T., and Nobre, A. C. (2006). Orienting attention to semantic categories. *Neuroimage* 33, 1178–1187. doi:10.1016/j.neuroimage.2006.08.017.

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., and Cabeza, R. (2008). Que PASA? The posterior-anterior shift in aging. *Cereb. Cortex* 18, 1201–9. doi:10.1093/cercor/bhm155.

De Deyne, S., & Storms G. (2008). Word associations: Norms for 1,424 Dutch Words in a continuous task, *Behav. Res. Methods*. http://ppw.kuleuven.be/concat/associations/

de Frias, C. M., Dixon, R. A., and Strauss, E. (2006). Structure of four executive functioning tests in healthy older adults. *Neuropsychology* 20, 206–214. doi:10.1037/0894-4105.20.2.206.

Derrfuss, J., Brass, M., Neumann, J., and Von Cramon, D. Y. (2005). Involvement of the inferior frontal junction in cognitive control: Meta-analyses of switching and stroop studies. in *Human Brain Mapping*, 22–34. doi:10.1002/hbm.20127.

Dubois, D., and Reshe-Rigon, P. (1995). De la «naturalité» des catégories sémantiques : des catégories «d'objets naturels» aux catégories lexicales. *Intellectica* 1, 33–66.

Duncan, J. (2006). EPS Mid-Career Award 2004: brain mechanisms of attention. *Q. J. Exp. Psychol. (Hove).* 59, 2–27. doi:10.1080/17470210500260674.

Fristoe, N. M., Salthouse, T. A., and Woodard, J. L. (1997). Examination of age-related deficits on the Wisconsin Card Sorting Test. *Neuropsychology* 11, 428–436. doi:10.1037/0894-4105.11.3.428.

Gevins, A., and Smith, M. E. (2000). Neurophysiological Measures of Working Memory and Individual Differences in Cognitive Ability and Cognitive Style. *Cereb. Cortex* 10, 829–839. doi:10.1093/cercor/10.9.829.

Goh, J. O., An, Y., and Resnick, S. M. (2012). Differential trajectories of age-related changes in components of executive and memory processes. *Psychol. Aging* 27, 707–19. doi:10.1037/a0026715.

Grady, C. L., Bernstein, L. J., Beig, S., and Siegenthaler, A. L. (2002). The effects of encoding task on age-related differences in the functional neuroanatomy of face memory. *Psychol. Aging* 17, 7–23. doi:10.1037/0882-7974.17.1.7.

Grady, C. (2012). The cognitive neuroscience of ageing. *Nat. Rev. Neurosci.* 13, 491–505. doi:10.1038/nrn3256.

Grady, C., Sarraf, S., Saverino, C., and Campbell, K. (2016). Age differences in the functional interactions among the default, frontoparietal control, and dorsal attention networks. *Neurobiol. Aging* 41, 159–172. doi:10.1016/j.neurobiolaging.2016.02.020.

Harding, I. H., Yücel, M., Harrison, B. J., Pantelis, C., and Breakspear, M. (2015). Effective connectivity within the frontoparietal control network differentiates cognitive control and working memory. *Neuroimage* 106, 144–153. doi:10.1016/j.neuroimage.2014.11.039.

Hazlett, E. A., Buchsbaum, M. S., Mohs, R. C., Spiegel-Cohen, J., Wei, T. C., Azueta, R., Haznedar, M. M., Singer, M. B., Shihabuddin, L., Luu-Hsia, C., et al. (1998). Age-related shift in brain region activity during successful memory performance. *Neurobiol. Aging* 19, 437–445. doi:10.1016/S0197-4580(98)00075-X.

Herd, S. A., O'Reilly, R. C., Hazy, T. E., Chatham, C. H., Brant, A. M., and Friedman, N. P. (2014). A neural network model of individual differences in task switching abilities. *Neuropsychologia* 62, 375–389. doi:10.1016/j.neuropsychologia.2014.04.014.

Hull, R., Martin, R. C., Beier, M. E., Lane, D., and Hamilton, A. C. (2008). Executive function in older adults: A structural equation modeling approach. *Neuropsychology* 224, 508–522. doi:10.1037/0894-4105.22.4.508.

Jefferies, E., and Lambon Ralph, M. A. (2006). Semantic impairment in stroke aphasia versus semantic dementia: a case-series comparison. *Brain* 129, 2132–47. doi:10.1093/brain/awl153.

Jenkinson, M., Bannister, P., Brady, M., and Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage* 17, 825–841. doi:10.1016/S1053-8119(02)91132-8.

Kopp, B., Lange, F., Howe, J., and Wessel, K. (2014). Age-related changes in neural recruitment for cognitive control. *Brain Cogn.* 85, 209–219. doi:10.1016/j.bandc.2013.12.008.

Lacombe, J., Jolicoeur, P., Grimault, S., Pineault, J., and Joubert, S. (2015). Neural changes associated with semantic processing in healthy aging despite intact behavioral performance. *Brain Lang.* 149, 118–127. doi:10.1016/j.bandl.2015.07.003.

Lambon Ralph, M. A., Jefferies, E., Patterson, K., and Rogers, T. T. (2016). The neural and computational bases of semantic cognition. *Nat. Rev. Neurosci.*, 1–14. doi:10.1038/nrn.2016.150.

Léger, L., Boumlak, H., and Tijus, C. (2008). BASETY: Extension et typicalité des exemplaires pour 21 catégories d'objets. *Can. J. Exp. Psychol.* 62, 223–232. doi:10.1037/a0012885.

Logan, J. M., Sanders, A. L., Snyder, A. Z., Morris, J. C., and Buckner, R. L. (2002). Under-recruitment and nonselective recruitment: Dissociable neural mechanisms associated with aging. *Neuron* 33, 827–840. doi:10.1016/S0896-6273(02)00612-8.

Maintenant, C., Blaye, A., and Paour, J.-L. (2011). Semantic categorical flexibility and aging: effect of semantic relations on maintenance and switching. *Psychol. Aging* 26, 461–6. doi:10.1037/a0021686.

Maintenant, C., Blaye, A., Pennequin, V., and Paour, J. L. (2013). Predictors of semantic categorical flexibility in older adults. *Br. J. Psychol.* 104, 265–282. doi:10.1111/j.2044-8295.2012.02116.x.

Martins, R., Simard, F., and Monchi, O. (2014). Differences between Patterns of Brain Activity Associated with Semantics and Those Linked with Phonological Processing Diminish with Age. *PLoS One* 9, e99710. doi:10.1371/journal.pone.0099710.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., and Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex

"Frontal Lobe" tasks: a latent variable analysis. *Cogn. Psychol.* 41, 49–100. doi:10.1006/cogp.1999.0734.

Monchi, O., Petrides, M., Petre, V., Worsley, K., and Dagher, A. (2001). Wisconsin Card Sorting Revisited: Distinct Neural Circuits Participating in Different Stages of the Task Identified by Event-Related Functional Magnetic Resonance Imaging. *J. Neurosci.* 21, 7733–7741. doi:21/19/7733 [pii].

Mudar, R. A., Chiang, H. S., Maguire, M. J., Spence, J. S., Eroh, J., Kraut, M. A., and Hart, J. (2015). Effects of age on cognitive control during semantic categorization. *Behav. Brain Res.* 287, 285–293. doi:10.1016/j.bbr.2015.03.042.

Murdoch, B. E. (2010). The cerebellum and language: Historical perspective and review. *Cortex* 46, 858–868. doi:10.1016/j.cortex.2009.07.018.

Nagel, I. E., Schumacher, E. H., Goebel, R., and D'Esposito, M. (2008). Functional MRI investigation of verbal selection mechanisms in lateral prefrontal cortex. *Neuroimage* 43, 801–7. doi:10.1016/j.neuroimage.2008.07.017.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., and Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* 53, 695–9. doi:10.1111/j.1532-5415.2005.53221.x.

Nelson, H. E. (1976). A modified card sorting test sensitive to frontal lobe defects. *Cortex A J. Devoted to Study Nerv. Syst. Behav.* 12, 313–324. doi:10.1016/S0010-9452(76)80035-4.

Nelson, D. L., McEvoy, C. L., and Schreiber, T. A. (2004). The University of South Florida free association, rhyme, and word fragment norms. *Behav. Res. Methods, Instruments, Comput.* 36, 402–407. doi:10.3758/BF03195588.

New, B., Pallier, C., and Ferrand, L. (2005). La documentation officielle de Lexique 3.

Niendam, T. A., Laird, A. R., Ray, K. L., Dean, Y. M., Glahn, D. C., and Carter, C. S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cogn Affect Behav Neurosci* 12, 241–268. doi:10.3758/s13415-011-0083-5.

Noonan, K. A., Jefferies, E., Corbett, F., and Lambon Ralph, M. A. (2010). Elucidating the nature of deregulated semantic cognition in semantic aphasia: evidence for the roles of prefrontal and temporo-parietal cortices. *J. Cogn. Neurosci.* 22, 1597–613. doi:10.1162/jocn.2009.21289.

Noonan, K. A., Jefferies, E., Visser, M., and Lambon Ralph, M. A. (2013). Going beyond inferior prefrontal involvement in semantic control: evidence for the additional contribution of dorsal angular gyrus and posterior middle temporal cortex. *J. Cogn. Neurosci.* 25, 1824–50. doi:10.1162/jocn_a_00442.

Noppeney, U., Phillips, J., and Price, C. (2004). The neural areas that control the retrieval and selection of semantics. *Neuropsychologia* 42, 1269–80. doi:10.1016/j.neuropsychologia.2003.12.014.

Oedekoven, C. S. H., Jansen, A., Kircher, T. T., and Leube, D. T. (2013). Age-related changes in parietal lobe activation during an episodic memory retrieval task. *J. Neural Transm.* 120, 799–806. doi:10.1007/s00702-012-0904-x.

Oldfield, R.C. (1971). The assessment and analysis of handedness : The Edinburg Inventory. Neuropsychologia 9 : 97-113. doi: 10.1016/0028-3932(71)90067-4

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., and Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychol. Aging* 17, 299–320. doi:10.1037/0882-7974.17.2.299.

Park, D. C., and Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annu. Rev. Psychol.* 60, 173–96. doi:10.1146/annurev.psych.59.103006.093656.

Paxton, J. L., Barch, D. M., Racine, C. a, and Braver, T. S. (2008). Cognitive control, goal maintenance, and prefrontal function in healthy aging. *Cereb. Cortex* 18, 1010–28. doi:10.1093/cercor/bhm135.

Peelle, J. E., Chandrasekaran, K., Powers, J., Smith, E. E., and Grossman, M. (2013). Age-related vulnerability in the neural systems supporting semantic processing. *Front. Aging Neurosci.* 5, 46. doi:10.3389/fnagi.2013.00046.

Reitan, R. M. (1955). The relation of the trail making test to organic brain damage. *- J Consult Psychol.* 19, 4. doi:10.1037/h0044509.

Reuter-Lorenz, P. A., and Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Curr. Dir. Psychol. Sci.* 17, 177–182. doi:10.1111/j.1467-8721.2008.00570.x.

Riis, J. L., Chong, H., Ryan, K. K., Wolk, D. A., Rentz, D. M., Holcomb, P. J., and Daffner, K. R. (2008). Compensatory neural activity distinguishes different patterns of normal cognitive aging. *Neuroimage* 39, 441–454. doi:10.1016/j.neuroimage.2007.08.034.

Rypma, B., Berger, J. S., and D'Esposito, M. (2002). The influence of working-memory demand and subject performance on prefrontal cortical activity. *J. Cogn. Neurosci.* 14, 721–31. doi:10.1162/08989290260138627.

Rypma, B., Berger, J. S., Prabhakaran, V., Martin Bly, B., Kimberg, D. Y., Biswal, B. B., and D'Esposito, M. (2006). Neural correlates of cognitive efficiency. *Neuroimage* 33, 969–979. doi:10.1016/j.neuroimage.2006.05.065.

Simard, F., Joanette, Y., Petrides, M., Jubault, T., Madjar, C., and Monchi, O. (2011). Fronto-striatal contribution to lexical set-shifting. *Cereb. Cortex* 21, 1084–93. doi:10.1093/cercor/bhq182.

Smith, S. M. (2002). Fast robust automated brain extraction. *Hum. Brain Mapp.* 17, 143–155. doi:10.1002/hbm.10062.

Spreng, R. N., Wojtowicz, M., and Grady, C. L. (2010). Reliable differences in brain activity between young and old adults: A quantitative meta-analysis across multiple cognitive domains. *Neurosci. Biobehav. Rev.* 34, 1178–1194. doi:10.1016/j.neubiorev.2010.01.009.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *J. Exp. Psychol.* 18, 643–662. doi:10.1037/h0054651.

Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., and Farah, M. J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. *Proc. Natl. Acad. Sci. U. S. A.* 94, 14792–7.

Valdois, S., Joanette, Y., Poissant, a, Ska, B., and Dehaut, F. (1990). Heterogeneity in the cognitive profile of normal elderly. *J. Clin. Exp. Neuropsychol.* 12, 587–96. doi:10.1080/01688639008401003.

Velanova, K., Lustig, C., Jacoby, L. L., and Buckner, R. L. (2007). Evidence for frontally mediated controlled processing differences in older adults. *Cereb. Cortex* 17, 1033–1046. doi:10.1093/cercor/bhl013.

Wagner, A. D., Maril, A., Bjork, R. A., and Schacter, D. L. (2001). Prefrontal Contributions to Executive Control: fMRI Evidence for Functional Distinctions within Lateral Prefrontal Cortex. *Neuroimage* 14, 1337–1347. doi:10.1006/nimg.2001.0936.

Walter, N., and Joanette, Y. (2007). The unnoticed contributions of the cerebellum to language. *Folia Phoniatr Logop* 59, 171-176. doi: 10.1159/000102928.

Ward Jr, J. H. (1963). Hierarchical Grouping to Optimize an Objective Function. *J. Am. Stat. Assoc.* 58, 236-244.

Wechsler, D. (1981). WAIS-R manual. The psychological corporation. *New York.*

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M. A., and Jefferies, E. (2011). The neural organization of semantic control: TMS evidence for a distributed network in left inferior frontal and posterior middle temporal gyrus. *Cereb. Cortex* 21, 1066–75. doi:10.1093/cercor/bhq180.

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M. a, and Jefferies, E. (2012). Executive semantic processing is underpinned by a large-scale neural network: revealing the contribution of left prefrontal, posterior temporal, and parietal cortex to controlled retrieval and selection using TMS. *J. Cogn. Neurosci.* 24, 133–47. doi:10.1162/jocn_a_00123.

Wierenga, C. E., Benjamin, M., Gopinath, K., Perlstein, W. M., Leonard, C. M., Rothi, L. J. G., Conway, T., Cato, M. A., Briggs, R., and Crosson, B. (2008). Age-related changes in word retrieval: Role of bilateral frontal and subcortical networks. *Neurobiol. Aging* 29, 436–451. doi:10.1016/j.neurobiolaging.2006.10.024.

Zysset, S., Schroeter, M. L., Neumann, J., and Yves von Cramon, D. (2007). Stroop interference, hemodynamic response and aging: An event-related fMRI study. *Neurobiol. Aging* 28, 937–946. doi:10.1016/j.neurobiolaging.2006.05.008.

Table 1: Means (M) and standard deviations (SD) of the demographic and neuropsychological variables of all participants (n = 40).

	Younger (n = 20)	**Older (n = 20)**		
	M (SD)	M (SD)	F (1.38)	*p-values*
Age	24.85 (3.85)	69.45 (4.54)	1129.02	.001
Gender (F: M)	16:4	17:3	0.603	.714
Education (years)	17.95 (2.52)	18.85 (2.88)	1.01	.301
Edinburgh inventory	95%	96%	0.89	.122
MoCA	28.6 (1.53)	28.7 (1.03)	0.058	.81
Stroop C	49.95 (6.88)	62.2 (9.12)	22.95	.001
Stroop W	39.25 (4.02)	45.30 (5.82)	14.61	.001
Stroop C–W	83.05 (13.42)	114.65 (22.29)	29.5	.001
TMT A	17.40 (4.35)	27.60 (8.22)	23.98	.001
TMT B	41.60 (11.77)	62.82 (16.29)	22.24	.001
Digits forward	10.5 (1.67)	9.65 (1.75)	2.46	.125
Digits backward	8.45 (2.03)	6.8 (1.73)	7.6	.009
Brixton (errors)	1.15 (1.03)	1.45 (1.05)	0.82	.37
WCST (errors)	0.88 (1.19)	1.05 (1.27)	0.41	.527
Semantic Fluency	39.70 (8.27)	28.85 (8.1)	17.55	.001

MoCA: Montreal Cognitive Assessment; Stroop-C: Stroop-Color; Stroop-W: Stroop-Word; TMT A & B: Trail Making Test A & B; WCST: Wisconsin Card Sorting Test

Table 2: Means (M) and standard deviation (SD) on the demographic and neuropsychological variables of the sample of older adults (n = 20) divided into two subgroups: updating-profile (n = 9) and shifting-profile (n = 11).

	Updating-profile	**Shifting-profile**		
	M (SD)	M (SD)	t (1.18)	*p-values*
Age	70.77 (4.96)	68.36 (4.08)	1.194	.248
Education (years)	18.44 (2.12)	19.18 (3.45)	-0.558	.584
MoCA	28.77 (0.97)	28.63 (1.12)	0.298	.769
Stroop C	65 (3.1)	59.90 (2.63)	-1.262	.223
Stroop W	46.33 (1.99)	44.45 (1.75)	-0.705	.490
Stroop C–W	112.88 (7.04)	116.09 (7.27)	0.314	.757
TMT A	24.55 (1.76)	30.09 (2.87)	1.552	.138
TMT B	52.11 (4.04)	71.54 (4.26)	3.259	.004
TMT B/A	2.25 (0.30)	2.55 (0.23)	0.799	.435
Digits forward	9.88 (0.58)	9.45 (0.54)	0.539	.596
Digits backward	7.88 (0.63)	5.99 (0.28)	3.039	.007
Brixton (errors)	2.11 (0.30)	0.90 (0.25)	-3.057	.007
WCST (errors)	1.88 (0.45)	0.36 (0.20)	-3.267	.004
Semantic fluency	24.88 (1.65)	32.09 (2.68)	-2.161	.044

MoCA: Montreal Cognitive Assessment; Stroop-C: Stroop-Color; Stroop-W: Stroop-Word; TMT A & B: Trail Making Test A & B; WCST: Wisconsin Card Sorting Test

Table 3: Behavioral performance (response times and correct responses) in word-matching task for 20 younger and 20 older adults.

	Younger	**Older**		
	Mean (SD)	Mean (SD)	F(1.38)	*p-values*
Response times (in milliseconds)				
Experimental condition				
Maintain rule	1217 (542)	1411 (383)*	1.704	.20
Switch rule	2365 (965)	2974 (793)	4.74	.036
Control condition	1048 (207)	1330 (166)	22.44	.001
Total correct responses (in %)	95.26 (5.30)	93.11 (7.51)	1.093	.302

SD: standard deviation

* control condition response time was subtracted from only maintain rule condition.

Table 4: Maintain rule minus control matching.

		MNI peak (mm)				
Cluster	**Anatomical areas**	**x**	**y**	**z**	**Z score**	**Voxel**
	Younger > Older					
	—					
	Older > Younger					
1	Left caudate nucleus	-6	18	-6	4.05	20788
	Right caudate nucleus	6	16	-1	4	
2	Left inferior parietal cortex (area 40)	–42	–60	31	4.05	23136
	Right posterior cingulate cortex (area 31)	18	–55	18	3.58	
	Left posterior cingulate cortex (area 31)	–16	–58	21	3.17	
3	Left cerebellum	–27	–83	–31	4	32824
	Right cerebellum	40	–65	–23	3.7	
	Right inferior temporal cortex (area 37)	46	–57	–22	3.69	
	Right occipital cortex (area 18)	11	–98	–11	3.64	

MNI : Montreal Neurological Institut

Table 5: Switch rule minus control matching.

		MNI peak (mm)				
Cluster	**Anatomical areas**	**x**	**y**	**z**	**Z score**	**voxel**
	Younger > Older					
	—					
	Older > Younger					
1	Left SMA (area 6)	–1	–5	48	3.41	16016
2	Left inferior parietal cortex (area 39/40)	–59	–28	31	3.33	16065
3	Right cerebellum	30	–68	–40	4.29	28680

MNI: Montreal Neurological, Institut; SMA: supplementary Motor Area

Table 6: Switch rule minus maintain rule.

		MNI peak (mm)				
Cluster	**Anatomical areas**	**x**	**y**	**z**	**Z score**	**voxel**
	Younger > Older					
1	Right SMA (area 6)	1	37	37	3.95	13342
	Right posterior prefrontal cortex (junction of 6, 8, and 44)	37	18	52	3.81	
	Older > Younger					
1	Left occipital cortex (area 19)	–26	–78	26	3.51	11648
	Left occipital cortex (area 18)	–11	–75	28	3.22	
2	Posterior cingulate cortex (area 31)	–12	–51	16	3.24	21623
	Left superior parietal cortex (area 7)	–12	–74	37	3.19	
	Left inferior parietal cortex (area 39)	–47	–67	28	3.13	

MNI: Montreal Neurological, Institut; SMA: supplementary Motor Area

Table 7: Behavioral performance (response times and correct responses) on the word-matching task for two older subgroups: updating-profile (n = 9) vs. shifting-profile (n = 11).

	Updating-profile	**Shifting-profile**		
	Mean (SD)	Mean (SD)	t(1.18)	*p-values*
Response times (in milliseconds)				
Experimental condition				
Maintain rule	2677 (453)	2818 (529)	-0.641	.529
Switch rule	3062 (994)	2901 (625)	-0.440	.665
Control condition	1341 (163)	1315 (178)	0.344	.735
Total correct responses (in %)	92.25 (7.67)	93.11 (6.37)	0.271	.789

SD: standard deviation

Table 8: Maintain rule minus control matching.

		MNI peak (mm)				
Cluster	**Anatomical areas**	**x**	**y**	**z**	**Z score**	**voxel**
1	**Updating-profile > Shifting-profile**					
	Left dorsolateral prefrontal cortex (area 9/46)	–45	14	45	2.86	96
	Shifting-profile > Updating- profile					
	—					

MNI: Montreal Neurological, Institut

Table 9: Switch rule minus control matching.

		MNI peak (mm)				
Cluster	**Anatomical areas**	**x**	**y**	**z**	**Z score**	**voxel**
	Updating-profile > Shifting-profile					
	—					
1	**Shifting-profile > Updating-profile**					
	Left inferior parietal cortex (area 39/40)	–45	–57	35	2.36	104

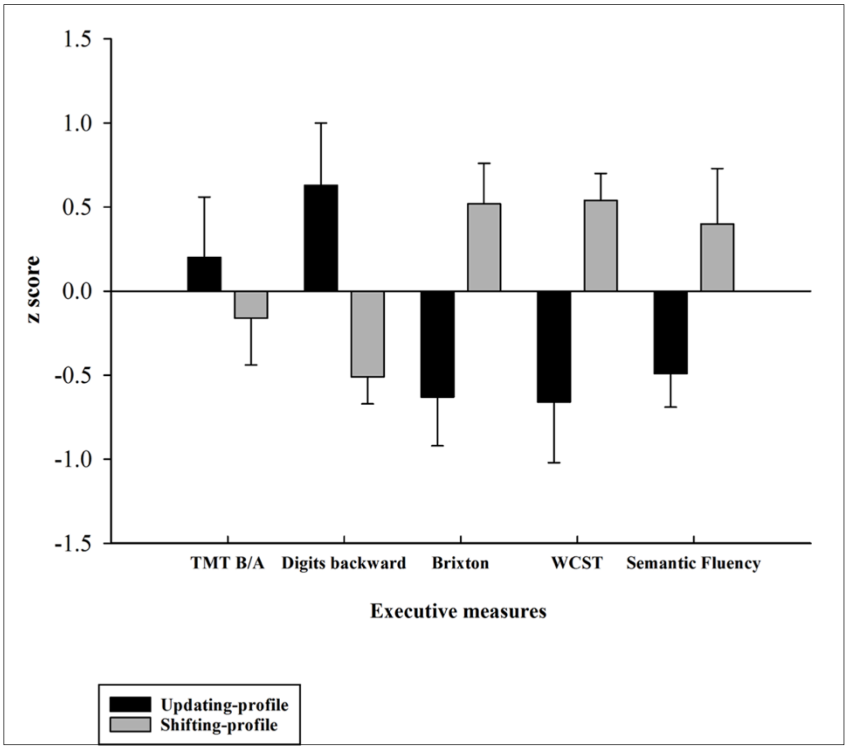

Figure 1. Z-executive scores of the two older subgroups (updating-profile vs. shifting-profile) based on five executive measures: TMT B/A, digits backward, number of errors on the Brixton test, number of errors on the WCST, number of words produced correctly on the semantic fluency task). Note: Tests for which increasing values in the original scores indexed lower performance were reversed in sign so that increasing values always reflected higher performance. Errors bars are represented by standard error mean values (SEM).

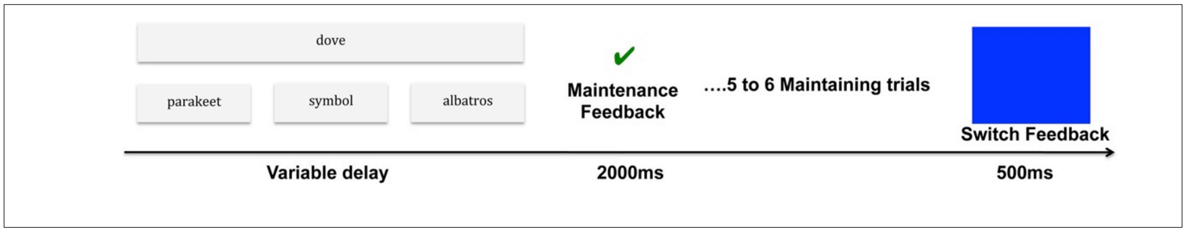

Figure 2. Experimental procedure of the word-matching task. In this example, each participant performed a task in which a target word presented at the top of the screen, dove (‘*colombe*’) had to be paired with one of three reference words, presented at the bottom, according to three possible semantic relationships: (a) typically related word (co-hyponyms) parakeet (‘*perruche*’); (b) atypically related word (co-hyponyms) albatross (‘*albatros*’); and (c) functionally related words (F) symbol (‘*symbole*’). The sorting period was followed by a maintenance feedback signal (green check mark displayed for 2000 ms) indicating that participants should maintain the same semantic rule as in the previous trial. After 5 or 6 maintaining trials, the rule changed (blue screen displayed for 500 ms) and participants had to discover the new classification rule and maintain it. As a control condition, a target card (e.g., AAAA) would be matched with the same sequence (e.g., aaaa) among three reference cards: aaaa, bbbb, cccc.

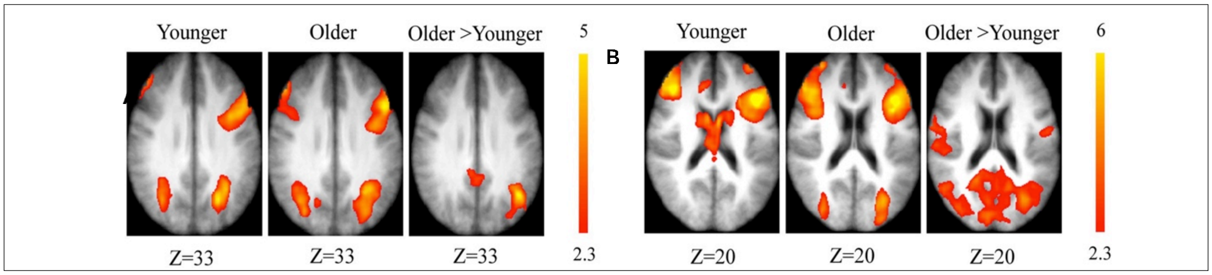

Figure 3. (A) Brain activation for maintain rule minus control condition. The younger group (cf. left). The older group (cf. middle). The comparison between the older adults and the younger adults (cf. right). The color scale represents the Z statistic. Z-values correspond to the coordinate of the axial plane. **(B) Brain activation for switch rule minus control condition.** The younger group (cf. left). The older group (cf. middle). The comparison between the older adults and the younger adults (cf. right).

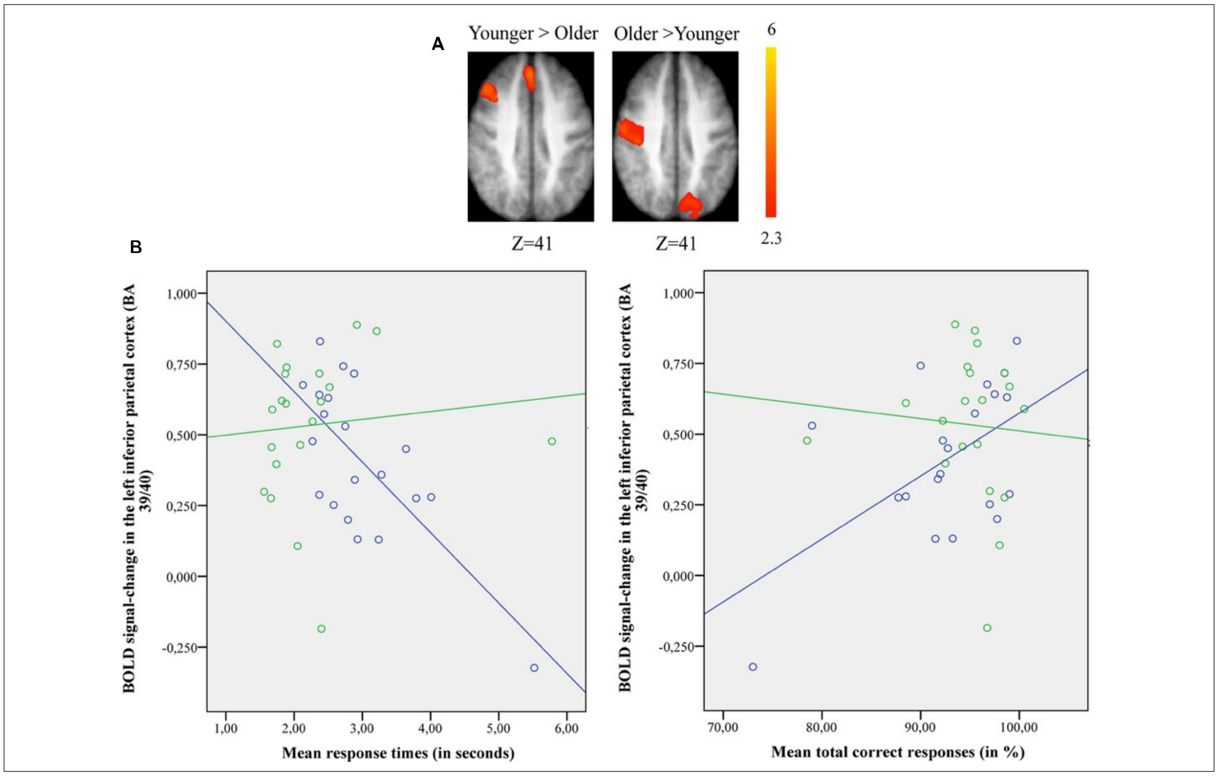

Figure 4. (A) Brain activation for performing switch rule relative to maintain rule for the younger adults compared to the older in the right posterior prefrontal cortex (cf. right) and in the left inferior parietal cortex in the older adults compared to the younger adults (cf. left). The color scale represents the Z statistic. Z-values correspond to the coordinate of the axial plane. **(B) Correlation between activation in the left inferior parietal cortex and behavioral measures for older (blue circles) and younger adults (green circles).** The left plot represents response times and the right plot the total correct responses for two groups. Note that correlation between behavioral measures and brain activity change in the right posterior prefrontal cortex did not reach any significant difference for two groups (not shown in this figure).

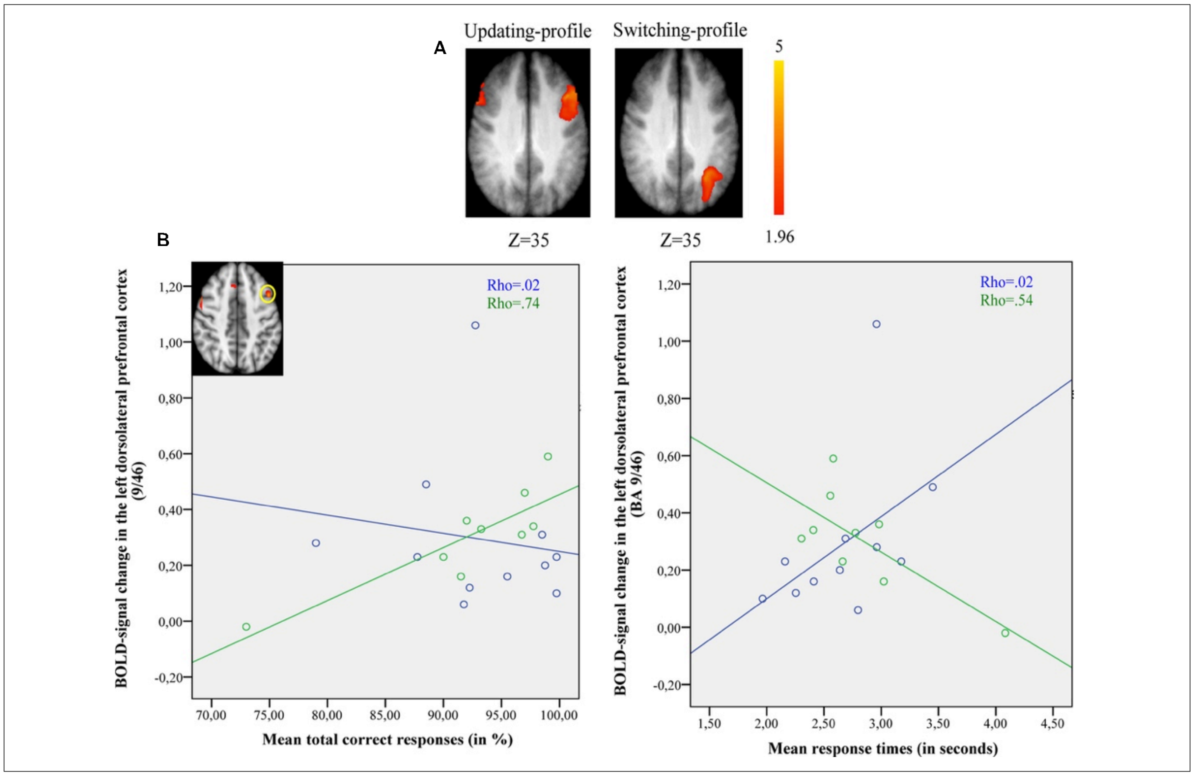

Figure 5. (A) Brain activation for maintain rule minus control matching. The updating-profile group (cf. left). The shifting-profile group (cf. right). The color scale represents the Z statistic. Z-values correspond to the coordinate of the axial plane. **(B) Correlation the left dorsolateral prefrontal cortex [BA 9/46; x = –42; y = 10; z = 35] and behavioral measures for the updating-profile group (green circles) and shifting-profile group (blue circles).** The left plot represents the total correct responses and the right plot mean response times. On the upper left, the updating-profile

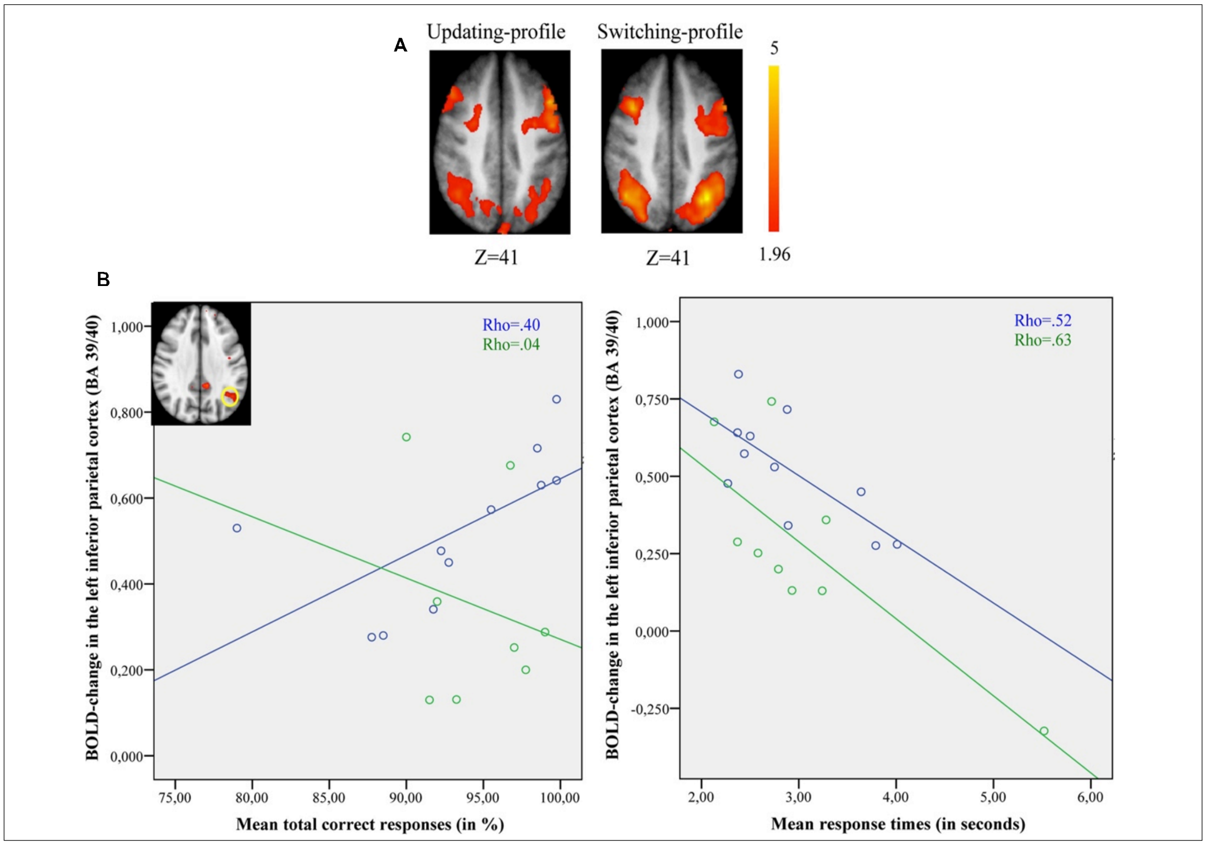

Figure 6. (A) Brain activation for switch rule minus control matching. The updating-profile group (cf. left). The shifting-profile group (cf. right). **(B) Correlation between the left inferior parietal cortex [BA 39/40; x = –33; y = –61; z = 39] and behavioral measures for the updating-profile group (green circles) and shifting-profile group (blue circles).** The left plot represents the total correct responses and the right plot the mean response times. On the upper left, the shifting-profile group shows significant activation in the left inferior parietal cortex (BA 39/40) compared to updating-profile group.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article//10.3389/fnagi.2017.00265/full#supplementary-material

1. Supplementary Tables

Table S1| Maintain rule minus control matching.

		MNI peak (mm)				
Cluster	**Anatomical areas**	**x**	**y**	**z**	**Z score**	**Voxels**
	Younger					
1	Right dorsolateral prefrontal cortex (area 9/46)	52	31	27	4.75	11013
	Right insula (area 41)	33	26	1	4.38	
2	Left inferior parietal (area 39)	–23	–67	36	4.98	26572
	Right superior parietal cortex (area 7)	35	–59	41	4.43	
	Left superior parietal cortex (area 7)	–21	–65	47	4.25	
3	Left posterior prefrontal cortex (junction of 6, 8, and 44)	–46	10	27	5.4	36766
	Left ventrolateral prefrontal cortex (area 44/45)	–42	24	18	5.25	
	Left lateral premotor cortex (area 6)	–37	5	28	5.14	
	Left insula (area 41)	–33	22	–2	4.42	
	Older					
1	Left inferior temporal cortex (area 37, 20)	–51	–49	–21	3.61	17812
	Left occipital cortex (area 18)	–27	–97	–14	3.47	
	Right cerebellum	58	20	21	3.32	
2	Right dorsolateral prefrontal cortex (area 9/46)	52	31	26	5.19	20501

	Right insula (area 41)	31	25	0	3.6	
	Left insula (area 41)	–31	21	0	3.57	
	Right posterior prefrontal cortex (junction of 6, 8, and 44)	52	16	26	3.51	
3	Left dorsolateral prefrontal cortex (area 9/46)	–43	15	25	5.57	40170
	Left posterior prefrontal cortex (junction of 6, 8, and 44)	–48	17	31	5.03	
	Left ventrolateral prefrontal cortex (area 44/45)	–41	23	19	4.59	
	Left lateral premotor cortex (area 6)	–40	3	28	4.54	
4	Left inferior parietal cortex (area 40)	–30	–58	38	5.53	40319
	Right superior parietal cortex (area 7)	37	–64	48	5.05	
	Left superior parietal cortex (area 7)	–31	–72	49	4.61	

MNI: Montreal Neurological, Institut

Table S2| Switch rule minus control matching.

		MNI peak (mm)				
Cluster	**Anatomical areas**	**x**	**y**	**z**	**Z score**	**voxel**
	Younger					
1	Left occipital cortex (BA 18)	–34	–90	–15	5.59	13630
2	Left superior parietal cortex (area 7)	–31	–59	47	5.86	49418
	Left inferior parietal cortex (area 39)	–23	–67	36	5.65	
	Right superior parietal cortex (area 7)	37	–58	54	5.48	
	Right inferior parietal cortex (area 39)	33	–60	40	5.18	
3	Left SMA (area 6)	–1	27	44	6.12	115940
	Left ventrolateral prefrontal cortex (area 44/45)	–42	23	20	6.06	
	Right dorsolateral prefrontal cortex (area 9/46)	45	29	24	5.8	
	Right posterior prefrontal cortex (junction of 6, 8, and 44)	39	18	49	5.76	
	Anterior cingulate cortex (area 32)	5	32	35	5.71	
4	Left caudate nucleus (head)	–5	16	–7	3.78	12257

	Right caudate nucleus (head)	6	–16	6	3.80	
	Older					
1	Right dorsolateral prefrontal cortex (area 9/46)	50	30	30	5.47	54820
	Right frontopolar (area 10)	35	57	4	5.09	
	Left frontopolar (area 10)	–49	37	–2	4.67	
	Right insula (area 41)	37	22	–5	3.7	
2	Left posterior prefrontal cortex (junction of 6, 8, and 44)	–42	15	26	6.63	81135
	Right superior parietal cortex (area 7)	39	–63	49	5.72	
	Left lateral premotor cortex (area 6)	–40	3	28	5.56	
	Left SMA (area 6)	–2	25	43	5.04	
	Right lateral premotor cortex (area 6)	28	5	50	5.04	
	Left insula (area 41)	–34	20	3	3.71	
3	Left inferior parietal cortex (area 40)	–30	–58	38	5.53	143491
	Right inferior parietal cortex (area 40)	42	–63	43	5.47	

MNI: Montreal Neurological, Institut; SMA: supplementary Motor Area

Table S3| Switch rule minus maintain rule

		MNI peak (mm)				
cluster	**Anatomical areas**	**x**	**y**	**z**	**Z score**	**voxel**
	Younger					
1	Left frontopolar cortex (area 10)	–34	57	–7	6.31	15779
2	Left occipital cortex (area 18)	–34	–92	–14	6.13	63839
3	Left superior parietal cortex (area 7)	–47	–51	45	7.04	67001
	Right superior parietal cortex (area 7)	44	–50	47	7.01	
	Right inferior parietal cortex (area 40)	46	–45	40	6.63	
4	Anterior cingulate cortex (area 32)	8	30	37	6.9	142136
	Right posterior prefrontal cortex (junction of 6, 8, and 44)	32	14	43	6.76	
	Right dorsolateral prefrontal cortex (area 9)	44	41	29	6.59	
	Older					
1	Left superior parietal cortex (area 7)	–17	–77	56	5.64	156442
	Left occipital cortex (area 18)	–25	–98	–13	5.59	
	Left inferior parietal cortex (area 40)	–45	–49	33	5.47	

	Right superior parietal cortex (area 7)	2	–74	53	5.3	
2	Left SMA (area 6)	–3	6	61	6.03	183731
	Left dorsolateral prefrontal cortex (area 9/46)	–41	21	29	5.84	
	Left frontopolar cortex (area 10)	–44	49	7	5.83	

MNI: Montreal Neurological, Institut; SMA: supplementary Motor Area

Table S4| Maintain rule minus control matching.

		MNI peak (mm)				
Cluster	**Anatomical areas**	**x**	**y**	**z**	**Z score**	**voxel**
	Updating-profile					
1	Left posterior prefrontal cortex (junction of 6, 8, and 44)	–44	14	24	4.14	21251
	Left ventrolateral prefrontal cortex (area 47/12)	–50	37	–4	4.09	
	Left dorsolateral prefrontal cortex (area 9/46)	–41	18	32	4.03	
	Left lateral premotor cortex (area 6)	–31	11	60	3.95	
2	Left cerebellum	–10	–89	–30	4.63	26118
	Right cerebellum	9	–89	–32	4.44	
	Shifting-profile					
1	Left inferior parietal cortex (area 40)	–29	–63	39	4.64	22400
	Left superior parietal cortex (area 7)	–28	–63	51	3.39	
2	Left inferior temporal cortex (area 20)	–36	–31	–24	3.40	23651

MNI: Montreal Neurological, Institut

Table S5| Switch rule minus control matching

		MNI peak (mm)				
Cluster	**Anatomical areas**	**x**	**y**	**z**	**Z score**	**voxel**
	Updating-profile					
1	Right lateral premotor cortex (area 6)	40	–3	60	3.71	39673
	Right dorsolateral prefrontal cortex (area 9/46)	30	42	11	3.66	
2	Left posterior prefrontal cortex (junction of 6, 8, and 44)	–42	12	29	4.45	44919
3	Left cerebellum	–10	–89	–30	4.63	128473
	Right cerebellum	9	–89	–32	4.44	
	Left superior parietal cortex (area 7)	–10	–69	60	4.03	
	Right occipital cortex (area 18)	30	–92	14	3.96	
	Left occipital cortex (area 18)	–25	–99	–13	3.95	
	Shifting-profile					
1	Right dorsolateral prefrontal cortex (area 9/46)	50	34	29	4.72	20635
	Right lateral premotor cortex (area 6)	33	17	52	3.61	
2	Left ventrolateral prefrontal cortex (area 44/45)	–41	26	13	4.4	40156

	Left posterior prefrontal cortex (junction of 6, 8, and 44)	–46	17	24	4.38	
	Right posterior prefrontal cortex (junction of 6, 8, and 44)	37	12	42	4.24	
	Left frontopolar cortex (area 10)	-38	51	12	4.24	
3	Right superior parietal cortex (area 7)	25	–73	53	5.55	136037
	Left inferior parietal cortex (area 39/40)	–33	–61	39	5.24	
	Right cerebellum	35	-66	-33	4.88	

MNI: Montreal Neurological, Institut; SMA: supplementary Motor Area

2. Supplementary data sheet

Word selection procedure

The experimental task required participants to sort words according to different levels of semantic relatedness. In order to construct the task, 169 stimulus words were chosen from the databases created by Dubois and Reshe-Rigon (1995*)* and Léger et al., (2008). The category ‘animals’ was selected (subcategories: birds, insects, quadrupeds, and fish). Before the final stimuli were presented to participants, a pilot study was carried out in which 40 volunteers (20 younger, M = 26.92 years; SD = 6.02 and 20 older, M = 60 years, SD = 5.75) were asked to identify the items they had never heard before in a list of words. Based on this assessment, items that were identified as unknown by three or more participants were excluded.

Afterwards, two types of semantic relatedness were also measured: typicality relatedness and functional relatedness. Two groups of 20 participants each (20 younger and 20 older) were asked to estimate the extent to which these words represented a category on a 7-point scale (1 = least typical; 7 = most typical). First, the typical and atypical words were selected following the consensus obtained by the two groups (Typical: younger: mean = 5.67, SD = 0.09; older: mean = 5.58, SD = 0.10; Atypical: younger: mean = 3.77, SD = 0.1; older: mean = 3.75, SD = 0.99). Then, from this selection, the moderately and highly typical words were selected and divided into two lists. The highly typical words were chosen as target words and presented to the same sample of participants in order to establish a list of functionally related words. For the last step in stimulus selection of functionally related words, a similar pilot study assessed the extent to which five words (databases of Nelson et al., 2004 and De Deyne and Storms, 2008) were strongly associated with each highly typical target word. All participants were instructed to read each highly typical word and then write down only the first five associated word that comes to mind immediatley. No time limit was placed on the participants, however they were encouraged to respond quickly. The dominant response is that produced by the largest number of participants was chosen in response to target word.

The final list contained 40 highly typical words, 40 moderately typical words, 40 atypical words and 40 functionally related words. None of the pilot participants were invited to participate in the experimental word-matching task. All stimuli were controlled for frequency, word length and imageability with the French lexical database Lexique 3, from Paris Descartes University, France (New et al., 2005; www.lexique.org). In terms of lexical frequency a significant difference was found between functional and atypical (M = 5.15, SD =1.3; M = 1.9 ; SD = 0.27; p = .016) and between moderately typical (M = 5.42, SD =1.18) and Atypical (p=.016). No significant difference was found between functional and typical (p=.142). No significant difference was found between moderately typical and functional (p = .142). In terms of degree of imageability a significant difference was found between functional and atypical ((M = 5.7, SD = 0.13; M = 4.9, SD =0.17; p = .002) and between moderately typical and atypical (M = 5.42 ; SD = 0.18; M = 4.9, SD =0.17; p=.081). No significant difference was found between functional and moderately typical (p=.384). In terms of word length, no significant difference was found between the three reference words [functional (M = 6.80, SD = 1.34), moderately typical (M = 6.60, SD = 1.49), atypical (M = 6.60, SD= 1.53), p = 0.78].

Control condition

Cible	Référence 1	Référence 2	Référence 3
AAAA	aaaa	uuuu	OOOO
EEEE	eeee	aaaa	UUUU
UUUU	uuuu	eeee	OOOO
OOOO	oooo	uuuu	AAAA

Experimental condition

Cible	Typique	Associé	Atypique
abeille	criquet	pollen	luciole
araignée	guêpe	phobie	scorpion
fourmi	libellule	colonie	grillon
moustique	criquet	piqure	scarabée
mouche	bourdon	tapette	tique
moustique	guêpe	piqure	cafard
fourmi	punaise	colonie	scarabée
abeille	punaise	pollen	scorpion
mouche	bourdon	tapette	scorpion
canard	geai	mare	autruche
aigle	canari	embleme	pélican
colombe	rossignol	symbole	buse
corbeau	mésange	presage	épervier
merle	corneille	mangeoire	albatros
moineau	faucon	graine	grue
mouette	serin	detritus	paon
perroquet	colibri	imitation	cane
canard	étourneau	mare	autruche
colombe	perruche	symbole	alouette
moineau	hibou	mangeoire	buse
mouette	pinson	detritus	cigogne
requin	sole	harpon	merlan
saumon	hareng	tartare	maquereau
truite	sole	grillade	anguille
sardine	brochet	boite	anguille
requin	carpe	harpon	raie
morue	thon	salage	piranha
sardine	hareng	boite	cachalot
vache	chimpanzé	elevage	hérisson
mouton	éléphant	bergerie	chacal
chat	lièvre	allergie	loutre
veau	kangourou	steak	babouin
chien	agneau	niche	blaireau

bœuf	panthère	hamburger	sanglier
cheval	girafe	caléche	mammouth
lion	brebis	jungle	taupe
ours	gorille	peluche	gazelle
cochon	léopard	ferme	furet
chèvre	guépard	barbiche	blaireau
tigre	jaguar	savane	mulot
loup	bison	meute	hérisson
lapin	buffle	carotte	chacal
cerf	chimpanzé	chasseur	mulot
renard	kangourou	agilité	sanglier
zébre	brebis	savane	mammouth
âne	guépard	fardeau	furet
renne	hamster	noel	loutre
chameau	biche	caravane	hérisson
souris	chevreuil	trappe	chacal
veau	éléphant	steak	antilope
renne	hamster	noel	blaireau
souris	chimpanzé	trappe	coyote
lion	agneau	jungle	taupe
cerf	girafe	chasseur	gazelle

CHAPITRE V : ARTICLE 3

Age-related Brain Activation Changes During Rule Repetition in Word-Matching

Ikram Methqal[1,4*], Basile Pinsard[1], Mahnoush Amiri[1] , Maximiliano A. Wilson[2], Oury Monchi[3], Jean-Sebastien Provost[3], Yves Joanette[1,4]

[1] Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal, Montreal, QC, Canada
[2] Centre de recherche CERVO - CIUSSS de la Capitale-Nationale et Département de réadaptation, Université Laval, Québec, Canada
[3] Department of Clinical Neurosciences, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Canada
[4] Faculty of Medicine, University of Montreal, QC, Canada

Publié dans la revue

Frontiers in Human Neurosciences

Contribution des auteurs

Ikram Methqal: conceptualisation de l'étude et de la méthodologie, recrutement de participants, expérimentation, passation des tests neuropsychologiques, passation session d'IRMf, préparation, extraction, analyse et interprétation des données IRMf, comportementales et neuropsychologiques, rédaction du manuscrit

Basile Pinsard: Élaboration d'une nouvelle méthode d'analyse IRMf et révision de l'article.

Mahnoush Amiri: contre-validation de la méthodologie d'analyse IRMf et revision d'article

Maximiliano A. Wilson: validation de conceptualisation de la méthodologie, contre-cotation des stimuli sélectionnés et révision de l'article

Oury Monchi: validation de la conceptualisation de la méthodologie, élaboration du logiciel de programmation d'analyse IRMf, révision de la méthodologie

Jean-Sebastien Provost : participation à la conceptualisation de la méthodologie, révision de la première version de la méthode d'analyse des données IRMf.

Yves Joanette: directeur de recherche, conceptualisation de l'étude et de la méthodologie, interprétation des résultats et révision du manuscrit.

Abstract

Objective: The purpose of this study was to explore the age-related brain activation changes during a word-matching semantic-category-based task, which required either repeating or changing a semantic rule to be applied. In order to do so, a word-semantic rule-based task was adapted from the Wisconsin Sorting Card Test, involving the repeated feedback-driven selection of given pairs of words based on semantic category-based criteria. **Method**: Forty healthy adults (20 younger and 20 older) performed a word-matching task while undergoing a fMRI scan in which they were required to pair a target word with another word from a group of three words. The required pairing is based on three word-pair semantic rules which correspond to different levels of semantic control demands: functional relatedness, moderately typical-relatedness (which were considered as low control demands), and atypical-relatedness (high control demands). The sorting period consisted of a continuous execution of the same sorting rule and an inferred trial-by-trial feedback was given. **Results**: Behavioral performance revealed increases in response times and decreases of correct responses according to the level of semantic control demands (functional vs. typical vs. atypical) for both age groups (younger and older) reflecting graded differences in the repetition of the application of a given semantic rule. Neuroimaging findings of significant brain activation showed two main results: 1) Greater task-related activation changes for the repetition of the application of atypical rules relative to typical and functional rules, and 2) Changes (older > younger) in the inferior prefrontal regions for functional rules and more extensive and bilateral activations for typical and atypical rules. Regarding the inter-semantic rules comparison, only task-related activation differences were observed for functional > typical (e.g. inferior parietal and temporal regions bilaterally) and atypical > typical (e.g. prefrontal, inferior parietal, posterior temporal, and subcortical regions).

Conclusion: These results suggest that healthy cognitive aging relies on the adaptive changes of inferior prefrontal resources involved in the repetitive execution of semantic rules, thus reflecting graded differences in support of task demands.

1. Introduction

In line with the comprehensive cognitive aging model developed by Craik and Bialystok (2006), the exploration of interactions between world knowledge and the executive control processes engaged in acting upon the world, do contribute to a better understanding of age-related cognitive and adaptive changes. In healthy aging, some cognitive domains decline with age, while many others, such as language abilities, remain well maintained throughout the lifespan (Park, 2002; Verhaghen, 2013). Specifically, older adults perform at least as similar as young adults in language comprehension and semantic processing, thus suggesting that semantic representation remains intact as we age (Pennequin et al., 2006; Maintenant et al., 2011). Moreover, there is consensus that aging has low impact on the organization of semantic knowledge as revealed by word associations and taxonomical categories (Wingfield and Stine-Morrow, 2000; Burke and Shafto, 2008). This organization is thought to be economical, being at the core of semantic knowledge acquisition and experience accumulation (Hedden and Gabrieli, 2004; Maintenant et al., 2011). Although many semantic aspects of language comprehension are spared, comprehension tasks that place high control process demands, mediated by prefrontal regions, might be more susceptible to age-related functional changes (Madden et al., 2012; Mudar et al., 2015; Diaz et al., 2016). However, investigation of age-related neurofunctional changes relevant to semantic control processing demands is scarce, as semantic processing is thought to be better preserved among the different components of language (Mayr and Kliegl, 2000; Federmeier and Kutas, 2005). More specifically, it is not clearly understood whether older adults show similar or different neural patterns to younger adults when faced with cognitive challenges in semantic tasks.

It is now well-established that cognitive abilities mediated by frontal regions are associated with dynamic/adaptive age-related neurofunctional changes even when performance is roughly similar for older and younger adults. Such neurofunctional reorganization patterns were captured in the *Hemispheric Asymmetry Reduction in OLDer adults* (HAROLD) hypothesis (Cabeza et al., 2002), as well as by the reported shift in activation from the occipito-temporal to frontal regions, known as the *Posterior-Anterior Shift in Aging* (PASA; Davis et al., 2008). In offering another comprehensive framework of age-related activation changes, the compensation-related utilization of neural circuits hypothesis model (CRUNCH, Reuter-Lorenz and Cappell, 2008) has been put forward to account for the task demands. According to this model, older adults show greater reliance on the inferior prefrontal regions at low levels of task demands, but as cognitive demands increase, limited neural resources are not sufficiently available to face a more complex cognitive challenge, resulting in a behavioral performance decline. Globally, these age-related neurofunctional changes can be conceived, at least partly, as the neurofunctional reorganization that allows the brain to sustain cognitive performance in older adults facing neurofunctional limitations. Alternatively, such neurofunctional changes could also represent the natural evolution of the neural bases of a cognitive system that enriches itself and evolves with age.

In language comprehension, it has been shown that to face an effortful retrieval and maintain a high level of performance, older adults show a greater inferior prefrontal activation than younger adults (Nielson et al., 2006; Wierenga et al., 2008; Martins et al., 2014). This suggests that neural changes underlying semantic control processes for tasks requiring cognitive demands upon these processes are taking place even as performance is maintained in older adults. Nevertheless, it remains valuable to explore if age-related brain activation changes can be observed during semantic categorization tasks, which exert much demand on effortful semantic processing.

Numerous neuroimaging studies have argued for a central role of the prefrontal region in cognitive control (Badre et al., 2005; Nagel et al., 2008; Spreng et al., 2010; Whitney et al., 2012). It is also thought to be a component of the semantic neural network underlying performance for semantic retrieval, or semantic working memory processes (Thompson-Schill et al., 1997; Wagner et al., 2001; Noonan et al., 2010). Consistent with this notion, repeated or continuous access to semantic-based knowledge appears to imply both semantic and cognitive control networks. In a meta-analysis of neuroimaging studies, Noonan et al., (2013) reported that executive-semantic processing in various language tasks modulates activations in bilateral brain networks, including the dorsolateral prefrontal cortex (PFC), ventrolateral (PFC) , inferior parietal cortex and posterior temporal cortex. Similarly, Hyafil and Koechlin (2016) found that the lateral prefrontal cortex contributes to executive control processes enabling a previously running task to be maintained for subsequent retrieval. They also provided evidence that prefrontal regions are relevant for executive-semantic processing when the rules retrieved from memory do not provide sufficient information to allow for a simple or easy execution of a task. This active rule maintenance represents a critical component of the cognitive control required for successful performance in semantic categorization tasks requiring for repetitive execution of a rule (Wagner et al., 2001; Noppeney et al., 2004; Noonan et al., 2010).

A current issue in cognitive neuroscience is the study of language processing and short-term memory (STM), for the maintenance of verbal information, as dependent cognitive systems, even if the properties of each system are unique. In that regard, Majerus (2013) put forward an integrative framework germane to the short-term maintenance of verbal information and the notion of repetition in language. Given the demands of rule-based categorization, category learning necessitates the ability to actively maintain a rule. At the same time, this rule requires language repetition in STM. Thus, effective rule use depends on demand from the rule itself placed on cognitive resources. Hence, increased rule complexity will exert a greater demand on verbal STM leaving insufficient cognitive resources available to successfully perform the task. This short-term maintenance in verbal tasks involves the temporary activation of semantic representation.

Another dimension to be considered in the repetition/application of a semantic rule is the complexity of the semantic relationship between the words. In healthy younger adults, for example, Lei et al., (2010), the use of an original deductive-category reasoning paradigm showed that the detection of an item’s category membership is associated with different processing times according to whether the semantic relationship between the words is typical (parrot-sparrow), or of an atypical relationship (parrot-ostrich). This result suggests that a stored representation of a given category requires greater cognitive control processes if it is less associated with the concept of the target category. Similarly, a recent study by Lopez-Zunini et al., (2014) reported that semantic decision is less effortful for words that share higher number of semantic features, or for those that are highly associated. Hence, relevant semantic information may be recruited in a top-down manner in semantic network because associated words could also be activated within neural semantic network. Interestingly, another fMRI-based finding (Jackson et al., 2015) proposes that the difference between categorical and associative relationships is more related to the level of control demand rather than the type of semantic relationship. Indeed, in categorical conditions by which the probe and target share many features, thus increasing executive demands, greater frontal activation was found as compared to associative condition. The results of this study also imply that associative and categorical relations of conceptual knowledge represent a unique and valuable dimension for manipulating task demands in language comprehension studies. These two types of semantic relationships appear to be associated with distinct levels of semantic control demands since it is known that there are also differences in executive-control processing of semantic associative and categorical relationships (Khateb et al., 2003; Kalénine et al., 2012; Mirman et al., 2017). Hence, semantic categorization represents a highly accurate and sensitive paradigm of the executive-semantic demands, which underlie cognitive processes, these being related to the nature of the semantic relationship. Taken together, these findings stress the importance of studying age-related neurofunctional reorganization during the repetition/application of semantic categorization rules.

The aim of this study was to describe age-related reorganization of the neurofunctional networks supporting semantic control demands during a word matching-task. A graded semantic strength of the functional/categorical semantic relationship between the words of a task was thought to allow a description of the neural and cognitive processes involved in the ability to repeat the application of a semantic rule, thus maintaining the continuous execution of given semantic relationships. More specifically, this study made use of a task asking for the application of either a new or already used (repeated) semantic categorisation rule in the context of a word-matching task. A word-semantic adaptation of the Wisconsin Card Sorting Test by (Monchi et al., 2001; Simard et al., 2011; Martins et al., 2014) asked either for the repeated use of a given semantic rule, after feedback indicating the maintenance of a categorical or functional relationship, or the use of another semantic rule. Three semantic rules based on categorical vs. functional relationships were used: (a) typically related words (co-hyponyms) (e.g., dove-parakeet); (b) atypically related words (co-hyponyms) (e.g., dove-albatross); and (c) functionally related words (e.g., dove-symbol). At the behavioral level, slower response times and less accurate responses were expected under higher (low-typical) semantic processing demands than under moderate (high-typical) and relatively low semantic processing demands (functional relatedness). Two main results were expected in line with the study's aim. First, and based on the literature reported, that the repetition of the application of a semantic rule based on an atypical co-hyponymic relationship (*atypical rule*) would be processed slower and less accurately than that of a typical (*typical rule)* or a functional (*functional rule*) semantic relationship. Under such conditions, larger clusters of brain activations would be observed in higher semantic control demand when an atypical rule is applied rather than typical and functional rules, regardless of the age group. With consideration to the CRUNCH model, the second expected result was that older adults would show a longer response time and less accuracy than younger participants for the atypical rule as compared to the typical and functional rules. From a neuroimaging perspective, we expect in older adults that they would exhibit larger brain activations in the prefrontal regions when faced with increased semantic processing demands (atypical rule). Also, and independently of age, it was expected that there would be semantic task-related differences in activation within the semantic control networks.

2. Material and Methods

2.1 Participants

Twenty healthy older adults aged between 63 and 80 and 20 younger adults whose ages ranged from 19 to 35 were recruited from a pool of volunteers at the Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal (CRIUGM). All participants were native French speakers and all were right-handed (scores greater than +95) as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). All had normal or corrected-to-normal vision; none had any history of major neurological disease, psychiatric illness, head injury, stroke, substance abuse, learning disabilities, or any problems that could interfere with behavior testing. Prior to the neuro-imaging session, all participants were also given a battery of neuro-psychological tests during a single 90-minute session which included: screening of global cognitive function (The Montreal Cognitive Assessment, MoCA; Nasreddine et al., 2005); the inhibition measure (Stroop Test; Stroop, 1935); the flexibility measure (Trail Making Test, TMT A and B; Reitan 1955); working memory measure (forward and backward Digit Span, WAIS III; Wechsler, 1981); several measures of ability to select a rule, maintain it, and switch to a new rule are from Burgess and Shallice (1997), for the Brixton test and Nelson (1976), for the Wisconsin Card Sorting Test (WCST); and semantic fluency as represented by the total number of words produced in 2 min for the category Animals (Cardebat et al., 1990). **Table 1** provides a detailed description of the raw cognitive measures as well as a statistical comparison of group means. Furthermore, the younger and the older adults' cognitive scores (not shown in **Table 1**) were within the average range according to all psychometric standardized data, suggesting normal cognitive functioning within the two groups. All participants gave written informed consent to the protocol, which was approved by the Institut universitaire de gériatrie de Montréal Human Ethics Committee and by the Regroupement Neuroimagerie/Québec (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.

2.2.1 Stimuli Selection

The experimental task required participants to sort words according to different levels of semantic relatedness. In order to construct the task, 169 stimulus words were chosen from the databases created by Dubois and Reshe-Rigon (1995*)* and Léger et al., (2008). The category ‘animals’ was selected (subcategories: birds, insects, quadrupeds, and fish). Before the final stimuli were presented to participants, a pilot study was carried out in which 40 volunteers (20 younger, M = 26.92 years; SD = 6.02 and 20 older, M = 60 years, SD = 5.75) were asked to identify the items they had never heard before in a list of words. Based on this assessment, items that were identified as unknown by three or more participants were excluded.

Afterwards, two types of semantic relatedness were also measured: typicality relatedness and functional relatedness. Two groups of 20 participants each (20 younger and 20 older) were asked to estimate the extent to which these words represented a category on a 7-point scale (1 = least typical; 7 = most typical). First, the typical and atypical words were selected following the consensus obtained by the two groups (Typical: younger: mean = 5.67, SD = 0.09; older: mean = 5.58, SD = 0.10; Atypical: younger: mean = 3.77, SD = 0.1; older: mean = 3.75, SD = 0.99). Then, from this selection, the moderately and highly typical words were selected and divided into two lists. The highly typical words were chosen as target words and presented to the same sample of participants in order to establish a list of functionally related words. For the last step in stimulus selection of functionally related words, a similar pilot study assessed the extent to which five words (databases of Nelson et al., 2004 and De Deyne and Storms, 2008) were strongly associated with each highly typical target word. All participants were instructed to read each highly typical word and then write down the first five associated words that immediately came to their minds. They were encouraged to respond as quickly as possible. However, no time limit was imposed to participants. The dominant response, i.e. the one produced by the largest number of participants, was chosen as the expected response for target words.

The final list contained 40 highly typical words (i.e. the target words), 40 moderately typical words, 40 atypical words and 40 functionally related words. None of the pilot participants were invited to participate in the experimental word-matching task. All stimuli were controlled for frequency, imageability and word length with the French lexical database Lexique 3 (New et al., 2005; www.lexique.org). In terms of lexical frequency a significant difference was found between functional and atypical (M = 5.15, SD =1.3; M = 1.9; SD = 0.27; p = .016) and between moderately typical and atypical (M = 3.2, SD = 0.5; M = 1.9; SD = 0.27; p = .037). No significant difference was found between functional and moderately typical (M = 5.15, SD =1.3; M = 5.42, SD = 1.18; p = .142). In terms of degree of imageability a significant difference was found between functional and atypical (M = 5.7, SD = 0.13; M = 4.9, SD = 0.17; p = .002) and between moderately typical and atypical (M = 5.42, SD = 0.18; M = 4.9, SD = 0.17; p = .081). No significant difference was found between functional and moderately typical (M = 5.7, SD = 0.13; M = 5.42, SD = 0.18; p = .384). In terms of word length, no significant difference was found between the three reference words [functional (M = 6.80, SD = 1.34), moderately typical (M = 6.60, SD = 1.49), atypical (M = 6.60, SD= 1.53), p = 0.78].

2.2.2 Task Procedure

The word-matching task used in this study was based on the computerized WCST developed and adapted to fMRI by Monchi et al. (2001) and Simard et al. (2011). The word-matching task was administered using stimulus presentation software (Media Control Function; Digivox, Montréal, Canada). Throughout the task, three reference cards based on three semantic rules were presented in a row at the bottom of the screen, displaying moderately, atypical, and functionally related words (see **Figure 1** for example). In each trial, a new target card was presented in the middle of the screen above the reference cards; it displayed a highly typical word. Participants must then match the target card with one of the reference cards based on moderately typical, atypical, or functional relatedness. Participants used a joystick to select among the three reference words, pressing left, right, or upward to select the reference word on the left, on the right, or in the middle, respectively.

The word-matching task trials contained two periods: matching and feedback.

- The matching period started with the presentation of a new target card (highly typical word). The participant then chose one of the three reference words by using one of the three joystick directions. The length of each matching period depended on the participant’s response times, which varied between 1470 and 4690 milli-seconds (ms) for this task. The period ended when the participant provided a selection response.
- The feedback period was indicated by a blue screen, which lasted for 500 ms and started as soon as a first correct match was made. Feedback was conveyed through a specific cue lasting for 2000 ms. An incorrect match was indicated by a red cross, whereas a correct match was indicated by a green check mark, which informed participants that the current matching rule was the correct one and that they should maintain the same rule as in the previous trial (see **Figure 1** for experimental procedure).
- In addition, there were control trials during which the target card was represented by a series of letters (e.g., AAAA), which was identical with one of the three reference cards (e.g., aaaa, bbbb, cccc). These trials involved pairing a target with an identical reference card (alphabetic association: AAAA with aaaa). No rule changes occurred in the control condition and control feedback indicated a correct or incorrect match.

All participants had one fMRI session, which consisted of four runs. Blocks of each of the four trials (the three semantic rule trials and the control trial) were presented in pseudo-random order four times per run. The rules changed without warning and the new correct rule would be applied and maintained until the participant achieved five to six consecutive correct matching trials (maintaining a rule if shown a green check mark) or had to switch it (if presented with a blue screen as feedback). It is worth mentioning that no participant reported learning the sequence regularity or having deduced the frequency of the changing rule. The control block consisted of eight trials. For each participant, the total number of trials per run changed according to performance, which depended on the number of errors. The participants were fully trained on the word-matching task by performing a block of conditions outside the scanner. Each participant needed to reach a performance level of 90% correct matching trials and have less than 5% of set-loss and perseverative errors before moving on to the scanning session.

The stimuli were presented via an LCD projector onto a mirror placed in front of the participant in the MRI scanner. Stimuli were outlined in black against a white background to improve visual contrast. All words were displayed horizontally at the top of the screen and were centred on a computer screen placed 50 cm away from the participant. The target word was placed in a larger rectangle and subtended a visual angle of 26.6° horizontally and 13.8° vertically. All words were presented in 28-point Arial font, and reference words were placed in three small rectangles 1.3 cm apart from each other.

With regard to the study purpose, only the correct (5 to 6) consecutive matching trials after the maintenance feedback period (henceforward referred to as rule repetition, for each semantic condition), was taken into account for behavioral and imaging analysis. Furthermore, to ensure that the new semantic rule was successfully acquired after a rule-matching change (related to the search for a correct rule), the first correct matching trial after switch feedback was removed. Several contrasts were generated for analysis by subtracting the control matching condition from the rule repetition condition for each of the three semantic rules as well as by subtracting the repetition of one semantic relationship type from another one. These contrasts are (1) repetition of the functional rule minus control condition; (2) repetition of the typical rule minus control condition; (3) repetition of the atypical rule minus control condition; (4) repetition of the functional rule minus typical rule; (5) repetition of the typical rule minus functional rule (6) repetition of the atypical rule minus typical rule; (7) repetition of the typical rule minus atypical rule. It should be noted that analysis performed for the contrast 5 and 7 did not show significant activation difference and for this reason are not reported in the present manuscript. For ease of description, and the pivotal interest of neuroimaging findings in healthy aging, only direct contrast comparison between older compared to the younger are reported in this manuscript. Nevertheless, the reverse contrast (younger compared to older) was also performed but did not elicit any significant difference in brain activation.

3. fMRI scanning

3.1 Image Acquisition

Participants were scanned at the Unité de Neuroimagerie Fonctionnelle of the Institut de Gériatrie de Montréal using a 3T Siemens Trio Magnetom MRI scanner (Siemens AG, Erlangen, Germany). The structural scan was a high-resolution T1-weighted 3D-MPRAGE, sagittal plane acquisition, field of view (FOV) = 256 mm, and matrix size = 256 x 256. In addition, we acquired functional images (T2* weighted, TR= 2500 ms, TE= 30 ms, 36 slices parallel to the anterior and posterior commissure (AC-PC) line, slice thickness = 3.5 mm with 3.5 mm^3 isotropic voxels, distance factor 0% (gap = 0 mm), Flip-angle = 90°, matrix = 64 x 64). Each 252-volume functional run lasted 10.5 min; four such runs were acquired for each participant. The stimulus presentation and the scanning were synchronized at the beginning of each run. To minimize head movement during scanning, cushions were placed between the subject's head and the coil.

3.2 Data analysis

FEAT (FMRI Expert Analysis Tool) Version 5.98, part of the FSL analysis package (FMRIB's Software Library, Version 4.1.4[3]), was used to conduct image pre-processing procedures. We corrected for head motion using MCFLIRT (FMRIB's motion correction linear image registration tool; Jenkinson et al., 2002), and also used the fsl_motion_outliers script to detect and remove any volumes with excessive head motion. Non-brain tissue was removed using BET (Brain Extraction Tool; Smith, 2002). Grand-mean intensity normalization was applied to the 4D dataset from each run based on multiplicative scaling factor. We applied a Gaussian kernel of 6 mm FWHM for spatial smoothing, and for temporal filtering, a high-pass filter was applied to remove low-frequency noise using Gaussian-weighted least-squares straight-line fitting (1/60 Hz). Temporal auto-correlation was corrected by using pre-whitening as implemented by FILM (FMRIB's improved linear model). Functional images of each participant were co-registered to structural images in native space, and structural images were normalized to Montreal Neurological Institute (MNI) standard space using FSL's MNI Avg 152 T1 2 x 2 x 2 mm. The same transformation matrices used for structural-to-standard transformations were then used for functional-to-standard space transformations of co-registered functional images.

The FEAT module in FSL was used for first level analysis. An event-related design was used to model the fMRI data, allowing for inference based on contrast. We included four different event types in the design matrix: functional, typical, and atypical rules; and control trials. The rule repetition period was defined on the basis of the time period, for which each length varied

---

[3] www.fmrib.ox.ac.uk/fsl

between trials depending on the participant’s response time. This period started with the presentation of a new trial and ended only when participant provided a selection response. The rule repetition period was convolved with a double-gamma hemodynamic response function (HRF). The aim was to explore all consecutive correct repetition rule periods for each semantic relationship (functional, typical and atypical).

A first-level GLM analysis was carried out separately for each run, including extended motion regressors generated from MCFLIRT estimates as confound variables. A between-subject GLM analysis was performed on first-level betas across the four runs to test for main-effect and age group brain activation differences during each semantic rule period (Functional, Typical and Atypical). Non-parametric statistical inference was applied with FSL Randomise (Nichols and Holmes, 2002) to correct for voxel-wise multiple comparisons and cluster-size, using threshold-free cluster enhancement (TFCE, Smith and Nichols, 2009). The latter process consists of fitting the between-subject GLM model performed with n=10000 sign flipping, and group permutation for main and group effects respectively, in order to generate a null distribution of both voxel-wise statistics and cluster-size. The resulting TFCE maps were at a threshold of $p<.05$ for display and extraction of clusters.

Behavioral data (response times and correct responses) were averaged for each group and for each of the three type of semantic rule (Functional vs. Typical vs. Atypical). A 3x2 ANOVA (semantic rules x age group) was performed using SPSS 15.0 for Mac. A comparison between the two groups for each semantic rule and between semantic rules for each group was done by ANOVAs.

4. Results

4.1 Behavioral Performance

4.1.1 Response Times

We conducted a 3x2 analysis of variance with the level of semantic control demands (Functional vs. Typical vs. Atypical) and the age group (Younger vs. Older) on the response times for repeating the application of semantic rule in word matching task (Table 2). There was a main effect of age group [$F(1.38) = 8.397$, $p < 0.01$] with response times being significantly longer in the older group than in the younger group. There was also significant main effect of semantic rule [$F(2.38) = 122.28$, $p < 0.001$], reflecting an increase in response times with a level of semantic control demand (Functional< Typical < Atypical). A planned comparison of level of semantic control demand shows significant difference between younger and older adults [Functional: $M_{older} = 2234$ ms, $SD = 467$; $M_{younger} = 1669$ ms, $SD = 390$; $F(1.38) = 17.182$, $p < 0.001$; Typical: $M_{older} = 2888$ ms, $SD = 490$; $M_{younger} = 2366$ ms, $SD = 755$; $F(1.38) = 6.704$, $p < 0.05$; Atypical: $M_{older} = 3103$ ms, $SD = 549$; $M_{younger} = 2559$ ms, $SD = 949$; $F(1.38) = 4.907$, $p < 0.05$]. Furthermore, a comparison between different semantic rules showed that younger adults as well as older adults tend to be faster during repeating the application of functional rule compared both to typical and to atypical rule [Younger: $F(2.57) = 8.098$, $p < 0.001$; Functional vs. Typical, $p < 0.05$; Functional vs. Atypical, $p < 0.001$; Older: $F(2.57) = 16.156$, $p < 0.001$; Functional vs. Typical, $p < 0.001$; Functional vs. Atypical, $p < 0.001$].

4.1.2 Correct Responses

The mean percentage of correct responses was considered as all correct consecutive repeating applications of the same semantic rule. A main effect of age group was found [$F(1.38) = 10.89$, $p < 0.01$] with percentage of correct response being significantly lower in the older adults than in the younger adults. There was also a significant main effect of semantic rule [$F(2.38) = 3.505$, $p < 0.05$], suggesting a decrease in percentage of correct responses with the level of semantic control demand. A planned comparison of level of semantic control demand shows significant difference of correct responses between younger and older adults only for rule repetition according to atypical condition ($p < 0.001$) (Table 2). A comparison between semantic rules showed that the younger adults as well as the older adults tend to perform accurately during repeating the application of semantic rules [Younger: $F(2.57) = 1.191$, $p = 0.311$; Older: $F(2.57) = 2.531$, $p = 0.42$].

4.2 Imaging Results

4.2.1 Level of Semantic Control Demands

We first explored task-related activation changes (Table 3, Figure 2A, B and C; two age groups together. We also investigated direct contrasts of brain activation between the two age groups (older compared to younger) associated to semantic control demands (Functional vs. Typical vs. Atypical) relative to control condition, (Table 4, 5 and 6; Figure 3A, B and C). As predicted, the neuroimaging analysis revealed age- and task-related activation changes associated with the repetition of semantic rule (Functional vs. Typical vs. Atypical) confirming the semantic processing demand manipulation was related to neurofunctional change when faced with a challenge insofar as it reflects the recruitment of additional neural resources. Indeed, age and task-related significant activation differences associated to semantic control demands were found in several parts of semantic control networks.

4.2.1.1 Task-related neurofunctional changes (all age groups together)

For the comparison of each experimental condition (functional, typical and atypical) with control condition (main task-effect), task-related activation changes were found, owing to semantic control demands (Table 3, Figure 2A, B and C). As predicted, significantly larger activation clusters were found in the higher level of semantic control demand represented by the atypical rule compared to typical and functional rules. This finding revealed that the semantic control network was differentially engaged depending on task demand as well as by unique functional contributions by specific brain regions within this network.

Indeed, significant activation clusters were consistently found by all experimental conditions regardless of whether the type of semantic rule is highly functional or more categorical (typical vs. atypical), when control condition was subtracted from experimental condition. This task-related activation (all age groups together) was found at the cerebellum bilaterally, the insula cortex (area 13), the inferior parietal cortex (area 39, angular gyrus), the occipital cortex (area 17) and the frontopolar cortex (area 10). However, patterns of activation associated to atypical rule were found to be more widespread than those for typical and functional.

Functional-related activation difference was found in the right dorsal medial PFC (area 8), the left posterior PFC (area 44), the right mid-dorsolateral PFC (area 9), the left inferior temporal cortex (area 37), the left dorsolateral PFC (area 46), the posterior middle temporal cortex bilaterally (area 21), the right superior parietal cortex (area 7), the right orbitofrontal cortex (area 11), the right lateral premotor cortex (area 6), and the left ventrolateral PFC (area 47). Subcortically, significantly greater activation was found in the right thalamus, caudate nucleus and in the left putamen.

Typical rule-related activation difference was found bilaterally in the dorsolateral PFC (area 9/46, 46), the left posterior PFC (area 44), the left lateral PFC (area 6), the left inferior temporal (area 37), the right superior parietal cortex (area 7), the left orbitofrontal (area 11), the left superior temporal cortex (area 22), the dorsal medial PFC bilaterally (area 8), the left ventrolateral PFC (area 47). Subcortically, significantly greater activation was found in the left globus pallidus.

In addition, differences in activation were also found for atypical rule repetition in additional brain regions including the right dorsal medial PFC (area 8), the posterior PFC (area 44) bilaterally, the right mid-dorsolateral PFC (area 9), the lateral premotor cortex (area 6) bilaterally, the right posterior cingulate cortex (area 23), the superior parietal cortex bilaterally (area 7), the left inferior temporal cortex (area 37), the left orbitofrontal cortex (area 11), the right inferior parietal cortex (area 40, supramarginal gyrus), the right posterior middle temporal cortex (are 21), and the left ventrolateral PFC (area 45). Subcortically, significant activation was observed bilaterally in the globus pallidus, the left thalamus, and in the right caudate nucleus.

4.2.1.2 Age-related Neurofunctional Changes

As predicted, the analysis of the interaction between task and age group revealed that the repetition of the application of a given semantic rule was driven by significant brain activation changes in healthy aging. Indeed, the older adults showed significant activation changes compared to the younger ones in the inferior prefrontal regions (frontopolar, orbitofrontal and ventrolateral PFC) revealing graded differences in the repetition of the application of a given semantic rule (Figure 3A, B and C).

For the inter-group comparison (older minus younger), the older adults showed significant activation changes compared to the younger adults for each semantic condition:

When functional was compared to the control condition (Table 4), significant activation of clusters was found in the frontopolar bilaterally (area 10), the left orbitofrontal cortex (area 11) and in the right ventrolateral PFC (area 47).

When typical was compared to control condition (Table 5), larger significant activation clusters were found bilaterally in the frontopolar cortex (are 10) as well as in the orbitofrontal cortex (area 11) and the ventrolateral PFC (area 47). Additionally, older adults (compared to the younger) further recruit additional brain regions including, the left dorsolateral PFC (area 46), the right dorsal medial PFC (area 8), the left lateral premotor cortex (area 6), the left superior parietal cortex (area 7), the left inferior parietal cortex (area 39 and 40, angular and supramarginal gyri, respectively), the left anterior cingulate cortex (area 24), the left posterior cingulate and the right occipital cortex (area 18).

When atypical was compared to control condition (Table 6), significant activation difference was observed bilaterally in the frontopolar (area 10), the orbitofrontal (area 11), the ventrolateral PFC (area 45 and 47), the left superior parietal cortex (area 70, the left inferior parietal cortex (area 39). In prefrontal cortex, bilaterally significant clusters in the dorsal medial PFC (area 8) and the lateral premotor cortex (area 6) were more recruited by older adults.

4.2.2 Inter-semantic Rules Comparisons

Differences in terms of brain activation changes for inter-semantic rules comparison based on the functional and categorical relationship (Functional vs. Typical and Atypical vs. Typical) are shown in Table 7 and 8, Figure 4 A and B.

4.2.2.1 Task-related Neuro-functional Changes

When functional was compared with typical rule repetition regardless of age groups (Table 7, Figure 4A), significantly stronger activation were found in the left frontopolar cortex (area 10), the inferior parietal cortex bilaterally (area 39 and 40, angular and supramarginal gyri, respectively), the superior temporal cortex bilaterally (area 22), the right posterior cingulate (area 31), the temporopolar bilaterally (area 38), the right orbitofrontal cortex (area 11), the left insula (area 13), the left anterior cingulate (area 32), the left superior parietal cortex (area 7), the mid-dorsolateral PFC (area 9), the left lateral premotor cortex (area 6), the dorsal medial PFC (area 8) and the left posterior middle temporal cortex (area 21). The reverse inter-rules comparison, i.e. typical > functional showed no significant activation difference.

When the atypical was compared to the typical rule repetition (Table 8, Figure 4B), significantly stronger activations were observed in the right dorsal-medial PFC (area 8), the inferior parietal cortex bilaterally (area 39 and 40, angular and supramarginal gyri, respectively), the right posterior cingulate cortex (area 31), the mid-dorsolateral PFC bilaterally (area 9), the right superior parietal cortex (area 7), the left anterior cingulate cortex (area 23), the right putamen, the right superior temporal cortex (area 22), the frontopolar cortex bilaterally (area 10), the right thalamus, the cerebellum bilaterally, the lateral premotor cortex (area 6), the right superior frontal cortex (area 6/8) the right inferior temporal cortex (area 37 and 20), the right occipital cortex (area 19) and the right posterior PFC (area 44). The reverse contrast i.e. typical > atypical showed no significant activation difference.

4.2.2.2 Age-related Neuro-functional Changes

No significant difference in activation was observed for the interaction between task-and age group (older minus younger or younger minus older).

5. Discussion

The aim of this study was to explore the age-related changes in patterns of brain activation underlying repetition of the application of a given semantic rule, using a word-matching task requiring different levels of semantic control demands (functional vs. typical vs. atypical). The main results point to differences in both behaviorally and neurofunctionally for the most semantic-control-demanding condition (atypical) for both younger and older participants (Table 2). However, even if performance was similar between younger and older participants, the latter group showed distinctive activation patterns. There was indeed a greater involvement of frontal regions for older adults in response to the increased demands, but this tended to decrease after having reached a certain level of high demand.

Regarding the first main result, both response times and the number of correct responses suggest that the implementation of an atypical rule of word-matching was a more difficult condition than typical and functional rule conditions for older and younger adults. This first result confirms that the different levels of semantic control demand we thought would be required for the application of the different semantic rules were indeed associated with distinct levels of cognitive difficulty. Consequently, this first result confirmed that the atypical rule does represent the most complex of the three rules used in our protocol. Of interest is how older adults responded more slowly and less accurately than younger adults for the repetition of the application of rules based on atypical relationship, and this despite also maintaining a relatively high level of correct responses (> 90%), comparable to that of their younger counterparts. This finding is in line with previous behavioral studies of semantic categorization (Roskies et al., 2001; Khateb et al., 2003; Lei et al., 2010; Wang et al., 2016) showing that word matching is executed faster when participants are asked to identify a close semantic relationship between two words than when this relationship is more distant. Logically, typical words within a category share more semantic features than atypical ones. The latter condition can then be considered more 'complex', the matching execution relying on more variable features, and would require higher semantic control. Automatic spreading of activation in semantic memory would facilitate the retrieval of features, as well as the rapid and less effortful identification of pairs of more prototypical concepts in a given category; meanwhile, additional control resources will be required to match pairs of words linked by a smaller number of shared semantic features, thus resulting in a longer time required to match the two less prototypical words of a given category (Jackson et al., 2015). In this respect, Lambon-Ralph and Jefferies (2016) suggest that semantic cognition is underpinned by the interaction of two components: semantic representations and executive-control process. The latter process plays a pivotal role in controlled retrieval of semantic information, such that relevant aspects of meaning are brought to the foreground. Converging neuroimaging findings provide evidence of a widely distributed neural network supporting semantic representation and executive-control processes (Whitney et al., 2011; Noonan et al., 2013). These two processes seem to contribute conjointly in executive-demanding semantic tasks (Whitney et al., 2011; Fedorenko et al., 2013; Davey et al., 2016). Consequently, and consistent with our first prediction, *the first main finding* reported here shows differences in the extent of activations in response to increased task demands within the semantic control network (Table 3). The repetition of the application of an atypical rule is associated with large activations in areas that have been shown consistently to be involved in high semantic control demands condition (Figure 2). Executive control over semantic processing thus appears to be supported by a common and distributed neural network including bilateral prefrontal cortex PFC (frontopolar, orbitofrontal, ventro-lateral PFC), inferior parietal cortex, insula, and extending posteriorly in the left superior temporal cortex as well as bilaterally in the occipital and cerebellum. Although these task-related activation clusters are found to be larger during the repetition of the application of atypical rule than for typical and functional rules, additional right lateralized activation is also observed in other parts of network including posterior prefrontal regions and subcortical regions (i.e caudate nucleus). The activation of the prefrontal, parietal and posterior temporal regions associated with semantic control across different semantic rules in the present study is indeed consistent with the view that these regions are of fundamental relevance in executive control across a wide range of cognitive domains (Noppeney et al., 2004; Whitney et al., 2009). Moreover, in the context of rule repetition as used in the present study, the PFC accounts largely for organizing goal-directed behavior, maintaining a previous task for subsequent retrieval and execution (frontopolar cortex; Hyafil and Koechlin, 2016), in reward-associated pair learning (orbitofrontal cortex, Robbins and Roberts, 2007), as well as for verbal rule acquisition and active retrieval from memory according to a rule (ventrolateral prefrontal cortex, Petrides and Pandya, 2002; Simard et al., 2011).

The activations reported herein for the inferior frontal area are therefore consistent with neurofunctional organization of the semantic/executive system, providing evidence that ventral aspects (i.e ventrolateral, BA 47; frontopolar BA 10; and orbitofrontal, BA11) contribute to controlled semantic retrieval, while selection is more sustained by the dorsal inferior frontal cortex (dorsolateral prefrontal, BA 46).

In line with our results, and as proposed by Davey et al., (2016), semantic control appears to be supported by at least two processes: a) First, a domain-general executive control sustained by a multiple domain network that allows for the goal-driven dimensions (application and maintenance) of the task (e.g feature-matching task; Duncan, 2010); b) Second, and automatic, an activation between strongly associated concepts within semantic system, independently from the executive control. Thus, the brain areas involved in semantic control as well as in the multiple-domain network would include dorsolateral prefrontal cortex, dorsal inferior frontal cortex, premotor cortex, parietal cortex and the posterior middle temporal cortex, and also the lateral occipital cortex. Given what is known about these areas, it is suggested that they are associated with the top-down allocation effort applied for task-demands.

A recent neuroimaging meta-analysis (Noonan et al., 2013) summarizes the brain regions within a semantic control network across many tasks requiring executive-semantic processing. The meta-analysis points to bilateral activations in the ventral and dorsal PFC, inferior parietal cortex, posterior middle temporal cortex and anterior cingulate cortex. For instance, when high-control semantic processing is required to resolve the ambiguity of accessing less frequent meanings of words, functional coupling has been observed in the PFC and the posterior middle temporal cortex. Moreover, these two brain regions also appear to be consistently involved in executively demanding goal-oriented tasks across cognitive domains, suggesting that they represent a non-specific 'multiple-demand network' (Davey et al., 2016). This suggests that the neural network supporting executive processing in the semantic domain overlaps with domain-general executive control. Beyond the contribution of the inferior prefrontal cortex in semantic control demand, there is also evidence for the additional contribution of inferior parietal cortex (angular gyrus) and posterior middle temporal cortex when semantic association strength is manipulated in the context of semantic similarity judgments (Wagner et al., 2001), or lexico-semantic categorization (Roskies et al., 2001). Specifically, increased activation in dorsal and ventral prefrontal cortices is associated with weak rather than strong semantic association. A recent fMRI study (Jackson et al., 2015) also reported graded activation differences associated with levels of semantic task difficulty. An example is the increased activation in the inferior frontal regions for the conceptual similarity judgment - the condition associated with the longest response time - compared to the associative similarity condition. Taken together, these results support the idea that the processing of conceptual semantic similarity activates the inferior frontal regions, as it requires more effortful semantic processing.

In summary, it appears that the task-related differences in activation reported here by reference to three levels of semantic relationships (functional, typical and atypical) does not reflect the difference in semantic relationship type itself, but rather increasing levels of difficulty of achieving the word-matching task. Indeed, the inter-semantic rules comparison performed in the present study shows relatively similar neurofunctional networks for all types of semantic relationship (Figure 4 A and B; Table 7 and 8) regardless of age, including the prefrontal, the inferior parietal and the temporal areas (anterior and posterior parts), all of them specifically involved in semantic control. This proposal is largely consistent with the results reported in a study conducted by Jackson et al. (2015).

Furthermore, the second main finding relates to a pattern of activation that occurs when the older adults were compared to the younger ones (Tables 4, 5 and 6). Our results show that some prefrontal regions are stronger activated in older participants in order to allow for good performance, even at the less demanding level of semantic control demand (Figure 3). This suggests that in order to cope with the task demand, the older adults recruit more executive neural resources as compared to the younger. This activation pattern suggests that the level of the strength of the association between the paired words impacts younger and older adults differently leading to additional cognitive control resources allocation by older participants. This result is compatible with what has been observed, and was predicted by reference to the CRUNCH model. Indeed, the older adults here engaged in the repetition of the application of all three semantic rules exhibit activations in the inferior prefrontal areas (frontopolar, orbitofrontal and ventrolateral PFC). Considering that our older adults group are very highly educated (an average of 17 years), the age-related brain activation changes are consistent with neuroimaging studies indicating that neurofunctional reorganization phenomenon tends to be observed at a cognitive level that is present mainly in well-educated individuals (Springer et al., 2005). Along these lines, some language studies have reported that greater fluency performance in older adults, relative to younger ones, might have been related to higher levels of education using broader vocabulary, underpinned by efficient strategies (e.g. Bolla, et al., 1990; Tombaugh, 1999; Kahlaoui et al., 2012). Other evidence resulting from the cognitive reserve concept (Stern, 2002, 2009) suggests a contribution from verbal proxies, owing to subjects having undergone years of formal education, of an efficient network selection which could take advantage of extensive neural resources. Similarly, Barulli and Stern (2013) have also reported that a higher cognitive reserve based on a high verbal intelligence quotient and years of education in healthy older adults reflects an ability to better neural resources allocation in successfully performing verbal tasks. On the basis of evidence showing knowledge-driven expertise through a life span, preservation of semantic processing could be associated with adaptive and unique neurofunctional patterns during healthy aging (Aine et al., 2006; Greenwood, 2007; Greenwood and Parasuraman, 2010; Cabeza, 2002). However, we believe that more studies are needed to clarify our understanding of the age-related executive processes in semantic tasks according to the level of education. The impact of level of education on the nature and extent of neurofunctional reorganization, according to different level of education (low vs. high) would be performed in the future aging studies.

In addition, we showed that, as semantic control demand increased across semantic relationship type (from functional to typical), the older adults exhibit activation of the inferior prefrontal regions at a greater extent than the younger in order to be able to cope with the increasing task-demands. Furthermore, the older adults were characterized by not only more frontal activation (left DLPFC and the right dorsal medial PFC) but also by activations of the posterior regions, including the left inferior parietal cortex (angular and supramarginal gyri) and the right occipital cortex. Considering a limited resource model in aging, a total amount of available processing resources is not what declines with age, but instead, the efficiency of the engaged neural resources. From a cognitive aging standpoint, some studies have even suggested that there is no age-related executive decline (Boone et al., 1990) and successful aging has been related to flexible and adaptive brain resources (Kramer et al., 1999; Adrover-Roig and Barcelo, 2010). These neurofunctional changes could be either the expression of adaptive neurofunctional patterns, or a possible evolution with age of the neurofunctional bases of semantic processing - which would increase emphasis upon the areas expressing differences in the strategies older adults used to resolve the task.

Beyond the activation of ventrolateral prefrontal, frontopolar and orbitofrontal areas, older adults also recruit the dorsal-medial prefrontal and lateral premotor areas to a greater extent, and bilaterally, in order to support increase task demands. Although more posterior regions (inferior parietal and occipital regions) are involved in the repetition of the application of the typical rule, older adults recruit additional prefrontal regions (dorso-medial cortex and lateral premotor), and these bilaterally when they are required to apply the atypical rule. There is also evidence that the atypical rule also contains an inhibitory control component, as the subjects have to suppress the dominant response to choose the item that is most closely related (Grossman et al., 2002; Noonan et al., 2013). Indeed, when typicality is low, a word-matching task requires more control of typicality processing to perform. The less typical the item the more taxing it would be to augment less salient semantic features suggesting high selection/inhibitory demands (Jefferies et al., 2013; Santi et al., 2016). Furthermore, the involvement of more extensive frontal activation in older adults could tend to express the requirement of more inhibitory control when typicality is low during word-matching.

In other words, older adults encounter their limited cognitive resources by recruiting extra prefrontal areas bilaterally. However, this adaptive neurofunctional reorganization appears to have its limits since it is observed that older adults with relatively healthy cognitive abilities appear to reach a critical threshold (CRUNCH phenomenon), after which there is a larger benefit of preserved semantic systems, under effortful semantic control conditions. These results are in accordance with the view that older adults appear to reach their capacity with increasing task demands probably because they become overwhelmed and then cease to effectively perform (Steffener et al., 2014).

Taken together, as more semantic control is required, these results point to a possible specificity of the neurofunctional basis of the complex relationship between the semantics of a word, and its relationship with the executive system. Indeed, whereas in most cognitive domains there seems to be a point at which a continuous increase in task demand reaches a saturation point, the increase in task demand for the semantic pairing of words appears to benefit from a shift from a more semantic control network (left VLPFC, left inferior parietal, occipital) to a more general, less specific executive control (e.g., dorso-medio-prefrontal bilaterally). This wider range of alternative possibilities could serve to explain the relative preservation of word semantic processing in aging.

As was suggested earlier, the current study reports age-related activation changes in the inferior prefrontal regions and the inferior parietal regions, associated with increased semantic control demands, which are consistent with previous studies (Roskies et al., 2001; Noonan et al., 2010). This neurofunctional network is part of a cognitive control network that is engaged when the task requires the participant to face a cognitive processing challenge (Kennedy et al., 2015). This capacity of the aging brain to mobilize the frontal and parietal regions necessary for highly demanding cognitive processes, such as increased semantic control demands, could represent the contribution of neurofunctional resources ranging from specific brain regions involved in maintaining semantic selection and controlled retrieval (inferior PFC, inferior parietal, anterior cingulate) (e.g. Binder et al., 2009; Noonan et al., 2013; Peelle et al., 2013), to more widespread recruitment of general-executive control brain areas (dorso-medial PFC and ventrolateral PFC bilaterally), the latter phenomenon having been shown to be consistently activated in cases of executive demands. As we age, neural resource engagement would shift from specific to more general neurofunctional networks, probably because the components of the network which are part of the more canonical semantic control networks have been involved to their full capacity. In line with this suggestion, Roskies et al., (2001) reported that activation of inferior prefrontal areas as modality-specific control regions might be subserving semantic decisions such as determining whether a certain criterion has been met. Thus, greater frontal contribution is reported when semantic relationship between words is ambiguous and requires the reactivation of semantic representations, or the selection of more attributes, thus putting more demands on the cognitive control system.

Intriguingly, in one study (Martins et al., 2014), the inferior prefrontal activations have not been considered as related to task-demands. These authors report neurofunctional changes in older adults when they match words after positive feedback. Dorsolateral prefrontal activation is reported when older participants perform both semantic and phonological rule matching. This similar pattern of neural activation is interpreted as a decrease in neurofunctional specificity with age. It should be noted that the semantic control manipulation demanded in the word-matching task reported here is greater than the demands of the Wisconsin Word Sorting Task used by Martins et al., (2014) to explore semantic and phonological processes. However, absence of brain activation differences concluded by these authors, when comparing different matching rules in the older group, could be explained neither by postulating decreased neurofunctional specificity, nor by distinct levels of their task demands. Therefore, in the present study, age-related neurofunctional reorganization is thought to underlie an ability of older adults to dynamically adapt neurofunctional resources to cope with task-demands.

In human cognition, language repetition helps to temporary maintain an information until a response is produced. As one of the most important concomitant factors to language rehabilitation, repetition promotes not only the learning or relearning of behaviors but also the maintenance of skills over time. The last decades of neuroplasticity research highlights the mechanisms that help create the appropriate and functional neural patterns to improve or restore a lost function (Kleim et al., 2008). Among these factors, rehearsal of a new learned or re-learned behavior triggers an adaptive neurofunctional reorganization in the healthy brain as well as after brain damage. More importantly, the results of the present study are in line with the integrative framework proposed by Majerus (2013) that put forth a valuable contribution of short-term maintenance and repetition of verbal information. While studying functional activation gives limited interpretation of how these functional regions are interconnected, the present findings could prospectively aid to further extend previous interpretations of short-term maintenance and repetition of semantic information during language processing.

Three findings of our study highlight this interpretation. Firstly, both language and verbal STM networks are involved during semantic rule repetition regardless of age. Importantly, active maintenance of 'complex' semantic representations (atypical semantic relationships) during rule repetition involves sub-cortical regions that support increasing load-effects in verbal STM. These findings largely support the notion of two distinct neural pathways for the maintenance and updating of information (Ekman et al., 2016). Secondly, a high task-demand impact differentially according to age on verbal STM network. More precisely, rather than in language networks, these differences are found in the neural patterns associated with domain-general executive control, including the left superior parietal cortex and the dorso-medial PFC (BA 8) bilaterally. Indeed, to ensure effective use of rules and also its active maintenance in STM, older adults recruit extensively the dorso-medial PFC to support this increase in the complexity of the semantic rule. This leads to a greater demand on STM. This assumption is coherent with the work of Fiebach et al., (2006) on short-maintenance of semantic information. The engagement of this functional brain region was reported in the monitoring of effort during ongoing processing required to keep active rule maintenance in STM in order to achieve semantic matching. Our results are in line with Fiebach et al.'s (2006) hypothesis of a frontally-guided activation of temporal semantic representations. These age-related neuro-functional changes within integrative networks help to sustain the notions of variability and dynamic systems as contributing to an understanding of cognitive and neural mechanisms that underlie adaptive changes in healthy cognitive aging.

Thirdly, during rule repetition, the ability of older adults to simply maintain a given rule in their verbal STM has also been reported to be preserved in previous studies (Martins et al., 2015). In the same vein, Kurth et al., (2016) reported increased activation in the dorsal PFC and inferior parietal sulcus (known as part of cognitive control network) with increased verbal STM load. More interestingly, their main findings argue against the notion that aging effects are supported by top- down process engagement. Although older adults showed less accurate and slower response time as activation increased in the dorsal fronto-parietal cortex, their performance compared to their younger counterparts suggests unimpaired ability to recruit top-down processes to face higher level-loads in verbal STM. Moreover, and consistent with our results, inferior frontal and parietal regions engagement in healthy aging seem to reflect that the cognitive control system is still dynamic and helpful during language comprehension tasks. As suggested by Fedorenko and Thompson-Schill, (2014), cognitive control is sometimes necessary and useful for successful language comprehension. According to this view, cognitive control resources would be implicated in preventing language loss in healthy aging (Wingfield et al., 2006; Hoyau et al., 2017). In sum, in the context of learning and rehabilitation, effortful cognitive processing may involve greater executive resources allocation, thus shedding light on the flexible and dynamic way in which cognitive control and language systems interact under high-level semantic processing.

6. Conclusion

The present study suggests that the age-related changes in the activation patterns associated with the repetitive application of a semantic rule in a word-matching task can be best accounted for by differences in the semantic control demands between semantic rules. The activation in the inferior prefrontal regions involved during the repetition of the application of a given semantic rule suggests that age-related activation changes in PFC could be observed, even if behavioral performance is maintained. These results are likely to reflect a flexible executive control system that allocates resources across specific cortical regions depending on the demands of semantic processing in language comprehension. Our findings are consistent with the view that neural patterns related to executive control processes support semantic performance in categorization tasks (Mudar et al., 2015). By reference to the CRUNCH model, high semantic control demands appear to be better supported by regions underlying domain-general aspects of cognition rather than language-specific processes. In this respect, our findings are consistent with semantic tasks studied for the high demands they place on executive control processes (Wagner et al., 2001; Whitney et al., 2009). At the same time, the age-related difference between associative and conceptual semantic similarity appears to be related to the extent of semantic control demand rather than to nature of the semantic relationship type. In fact, the differences in activation between the different types of semantic relations used in the present study are also consistent with the hypothesis that this distinction lies in the dynamic coordination of different activation patterns rather than being related to specific brain regions (Mirman et al., 2017). It is clear how the simple repetition of the application of a semantic word-matching rule reveals much about the function of the aging brain and its ability to categorize the world, semantically, through its words.

Acknowledgments

The first author is grateful to Michel Bteich for his relevant comments on earlier versions of this manuscript and recent discussions related to it.

References

Adrover-Roig, D., and Barceló, F. (2010). Individual differences in aging and cognitive control modulate the neural indexes of context updating and maintenance during task switching. *Cortex.* 46, 434–50. doi:10.1016/j.cortex.2009.09.012.

Aine, C. J., Woodruff, C. C., Knoefel, J. E., Adair, J. C., Hudson, D., Qualls, C., Bockholt, J., Best, E., Kovacevic, S., Cobb, W., et al. (2006). Aging: Compensation or maturation? *Neuroimage* 32, 1891–1904. doi:10.1016/j.neuroimage.2006.05.005.

Badre, D., Poldrack, R. A., Paré-Blagoev, E. J., Insler, R. Z., and Wagner, A. D. (2005). Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. *Neuron* 47, 907–918. doi:10.1016/j.neuron.2005.07.023.

Barulli, D., and Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. *Trends in Cognitive Sciences*, 17, 502–509. doi.org/10.1016/j.tics.2013.08.012

Binder, J. R., Desai, R. H., Graves, W. W., and Conant, L. L. (2009). Where Is the Semantic System? A Critical Review and Meta-Analysis of 120 Functional Neuroimaging Studies. *Cereb. Cortex* 19, 2767–2796. doi:10.1093/cercor/bhp055.

Bolla, K. I., Lindgren, K. N., Bonaccorsy, C., and Bleecker, M. L. (1990). Predictors of verbal fluency (FAS) in the healthy elderly. *J. Clin. Psychol.* 46, 623–628. doi:10.1002/1097-4679(199009)46:5<623::AID-JCLP2270460513>3.0.CO;2-C.

Boone, K. B., Miller, B. L., Lesser, I. M., Hill, E., and D'Elia, L. (1990). Performance on frontal lobe tests in healthy, older individuals. *Dev. Neuropsychol.* 6, 215–223. doi:10.1080/87565649009540462.

Burgess, P.W. and Shallice, T. The Hayling and Brixton Tests. Bury St.Edmunds, UK: Thames Valley Test Company, 1997.

Burke, D. M., and M. A. Shafto. 2008. Language and aging. The Handbook of Aging and Cognition, ed. by F. I. M. Craik, and T. A. Salthouse, 373–443. New York: Psychology Press

Cabeza, R., Anderson, N. D., Locantore, J. K., and McIntosh, A. R. (2002). Aging Gracefully: Compensatory Brain Activity in High-Performing Older Adults. *Neuroimage* 17, 1394–1402. doi:10.1006/nimg.2002.1280.

Cardebat, D., Doyon, B., Puel, M., Goulet, P., & Joanette, Y. (1990). Formal and semantic lexical evocation in normal subjects. Performance and dynamics of production as a function of sex, age and educational level. Acta Neurologica Belgica, 90(4), 207–217. doi: PMID 2124031.

Craik, F. I. M., and Bialystok, E. (2006). Cognition through the lifespan: Mechanisms of change. *Trends Cogn. Sci.* 10, 131–138. doi:10.1016/j.tics.2006.01.007.

Davey, J., Thompson, H. E., Hallam, G., Karapanagiotidis, T., Murphy, C., De Caso, I., Krieger-Redwood, K., Bernhardt, B. C., Smallwood, J., and Jefferies, E. (2016). Exploring the role of the posterior middle temporal gyrus in semantic cognition: Integration of anterior temporal lobe with executive processes. *Neuroimage* 137, 165–177. doi:10.1016/j.neuroimage.2016.05.051.

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., and Cabeza, R. (2008). Qué PASA? the posterior-anterior shift in aging. *Cereb. Cortex* 18, 1201–1209. doi:10.1093/cercor/bhm155.

De Deyne, S., & Storms G. (2008). Word associations: Norms for 1,424 Dutch Words in a continuous task, *Behav. Res. Methods*. http://ppw.kuleuven.be/concat/associations/

Diaz, M. T., Rizio, A. A., and Zhuang, J. (2016). The neural language systems that support healthy aging: Integrating function, structure, and behavior. *Lang. Linguist. Compass* 10, 314–334. doi:10.1111/lnc3.12199.

Dubois, D., and Reshe-Rigon, P. (1995). De la «naturalité» des catégories sémantiques : des catégories «d'objets naturels» aux catégories lexicales. *Intellectica* 1, 33–66.

Duncan, J. (2010). The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends Cogn. Sci.* 14, 172–179. doi:10.1016/j.tics.2010.01.004.

Ekman, M., Fiebach, C. J., Melzer, C., Tittgemeyer, M., and Derrfuss, J. (2016). Different Roles of Direct and Indirect Frontoparietal Pathways for Individual Working Memory Capacity. *J. Neurosci.* 36, 2894–2903. doi:10.1523/JNEUROSCI.1376-14.2016.

Federmeier, K. D., and Kutas, M. (2005). Aging in context: Age-related changes in context use during language comprehension. *Psychophysiology* 42, 133–141. doi:10.1111/j.1469-8986.2005.00274.x.

Fedorenko, E., Duncan, J., and Kanwisher, N. (2013). Broad domain generality in focal regions of frontal and parietal cortex. *Proc. Natl. Acad. Sci. U. S. A.* 110, 16616–21. doi:10.1073/pnas.1315235110.

Fedorenko, E., and Thompson-Schill, S. L. (2014). Reworking the language network. *Trends Cogn. Sci.* 18, 120–127. doi:10.1016/j.tics.2013.12.006.

Fiebach, C. J., Rissman, J., and D'Esposito, M. (2006). Modulation of Inferotemporal Cortex Activation during Verbal Working Memory Maintenance. *Neuron* 51, 251–261. doi:10.1016/j.neuron.2006.06.007.

Greenwood, P. M. (2007). Functional plasticity in cognitive aging: review and hypothesis. *Neuropsychology* 21, 657–673. doi:10.1037/0894-4105.21.6.657.

Greenwood, P. M., and Parasuraman, R. (2010). Neuronal and cognitive plasticity: A neurocognitive framework for ameliorating cognitive aging. *Front. Aging Neurosci.* 2, 1–14. doi:10.3389/fnagi.2010.00150.

Grossman, M., Smith, E. E., Koenig, P., Glosser, G., DeVita, C., Moore, P., and McMillan, C. (2002). The Neural Basis for Categorization in Semantic Memory. *Neuroimage* 17, 1549–1561. doi:10.1006/nimg.2002.1273.

Hedden, T., and Gabrieli, J. D. E. (2004). Insights into the ageing mind: a view from cognitive neuroscience. *Nat. Rev. Neurosci.* 5, 87–96. doi:10.1038/nrn1323.

Hoyau, E., Boudiaf, N., Cousin, E., Pichat, C., Fournet, N., Krainik, A., Jaillard, A., and Baciu, M. (2017). Aging modulates the hemispheric specialization during word production. *Front. Aging Neurosci.* 9. doi:10.3389/fnagi.2017.00125.

Hyafil, A., and Koechlin, E. (2016). A neurocomputational model of human frontopolar cortex function. *bioRxiv*, 37150. doi:10.1101/037150.

Jackson, R. L., Hoffman, P., Pobric, G., and Ralph, M. A. L. (2015). The nature and neural correlates of semantic association versus conceptual similarity. *Cereb. Cortex* 25, 4319–4333. doi:10.1093/cercor/bhv003.

Jefferies, E. (2013). The neural basis of semantic cognition: Converging evidence from neuropsychology, neuroimaging and TMS. *Cortex* 49, 611–625. doi:10.1016/j.cortex.2012.10.008.

Jenkinson, M., and Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Med. Image Anal.* 5, 143–156. doi:10.1016/S1361-8415(01)00036-6.

Kahlaoui, K., Sante, G. Di, Barbeau, J., Maheux, M., Lesage, F., Ska, B., & Joanette, Y. (2012). Contribution of NIRS to the study of prefrontal cortex for verbal fluency in aging. *Brain and Language*, *121*, 164–173. doi.org/10.1016/j.bandl.2011.11.002

Kalénine, S., Mirman, D., and Buxbaum, L. J. (2012). A Combination of Thematic and Similarity-Based Semantic Processes Confers Resistance to Deficit Following Left Hemisphere Stroke. *Front. Hum. Neurosci.* 6, 1–12. doi:10.3389/fnhum.2012.00106.

Kennedy, K. M., Rodrigue, K. M., Bischof, G. N., Hebrank, A. C., Reuter-Lorenz, P. A., and Park, D. C. (2015). Age trajectories of functional activation under conditions of low and high processing demands: An adult lifespan fMRI study of the aging brain. *Neuroimage* 104, 21–34. doi:10.1016/j.neuroimage.2014.09.056.

Khateb, A., Michel, C. M., Pegna, A. J., O'Dochartaigh, S. D., Landis, T., and Annoni, J. M. (2003). Processing of semantic categorical and associative relations: An ERP mapping study. *Int. J. Psychophysiol.* 49, 41–55. doi:10.1016/S0167-8760(03)00076-X.

Kleim, J. A., and Jones, T. A. (2008). Principles of Experience-Dependent Neural Plasticity: Implications for Rehabilitation After Brain Damage. *J. Speech Lang. Hear. Res.* 51, S225. doi:10.1044/1092-4388(2008/018).

Kramer, A. F., Hahn, S., and Gopher, D. (1999). Task coordination and aging: explorations of executive control processes in the task switching paradigm. *Acta Psychol. (Amst).* 101, 339–378. doi:10.1016/S0001-6918(99)00011-6.

Kurth, S., Majerus, S., Bastin, C., Collette, F., Jaspar, M., Bahri, M. A., and Salmon, E. (2016). Effects of aging on task- and stimulus-related cerebral attention networks. *Neurobiol. Aging* 44, 85–95. doi:10.1016/j.neurobiolaging.2016.04.015.

Lacombe, J., Jolicoeur, P., Grimault, S., Pineault, J., and Joubert, S. (2015). Neural changes associated with semantic processing in healthy aging despite intact behavioral performance. *Brain Lang.* 149, 118–127. doi:10.1016/j.bandl.2015.07.003.

Lambon Ralph, M. A., Jefferies, E., Patterson, K., and Rogers, T. T. (2016). The neural and computational bases of semantic cognition. *Nat. Rev. Neurosci.*, 1–14. doi:10.1038/nrn.2016.150.

Léger, L., Boumlak, H., and Tijus, C. (2008). BASETY: Extension et typicalité des exemplaires pour 21 catégories d'objets. *Can. J. Exp. Psychol.* 62, 223–232. doi:10.1037/a0012885.

Lei, Y., Li, F., Long, C., Li, P., Chen, Q., Ni, Y., and Li, H. (2010). How does typicality of category members affect the deductive reasoning? An ERP study. *Exp. Brain Res.* 204, 47–56. doi:10.1007/s00221-010-2292-5.

López Zunini, R., Muller-Gass, A., and Campbell, K. (2014). The effects of total sleep deprivation on semantic priming: Event-related potential evidence for automatic and controlled processing strategies. *Brain Cogn.* 84, 14–25. doi:10.1016/j.bandc.2013.08.006.

Madden, D. J., Bennett, I. J., Burzynska, A., Potter, G. G., Chen, N., and Song, A. W. (2012). Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. *Biochim. Biophys. Acta - Mol. Basis Dis.* 1822, 386–400. doi:10.1016/j.bbadis.2011.08.003.

Majerus, S. (2013). Language repetition and short-term memory: an integrative framework. *Front. Hum. Neurosci.* 7, 1–16. doi:10.3389/fnhum.2013.00357.

Maintenant, C., Blaye, A., and Paour, J.-L. (2011). Semantic categorical flexibility and aging: effect of semantic relations on maintenance and switching. *Psychol. Aging* 26, 461–6. doi:10.1037/a0021686.

Martins, R., Simard, F., and Monchi, O. (2014). Differences between Patterns of Brain Activity Associated with Semantics and Those Linked with Phonological Processing Diminish with Age. *PLoS One* 9, e99710. doi:10.1371/journal.pone.0099710.

Mayr, U., and Kliegl, R. (2000). Complex semantic processing in old age: does it stay or does it go? *Psychol. Aging* 15, 29–43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10755287.

Mirman, D., Landrigan, J.-F., and Britt, A. E. (2017). Taxonomic and thematic semantic systems. *Psychol. Bull.* 143, 499–520. doi:10.1037/bul0000092.

Monchi, O., Petrides, M., Petre, V., Worsley, K., and Dagher, A. (2001). Wisconsin Card Sorting Revisited: Distinct Neural Circuits Participating in Different Stages of the Task Identified by Event-Related Functional Magnetic Resonance Imaging. *J. Neurosci.* 21, 7733–7741. doi:21/19/7733 [pii].

Mudar, R. A., Chiang, H. S., Maguire, M. J., Spence, J. S., Eroh, J., Kraut, M. A., and Hart, J. (2015). Effects of age on cognitive control during semantic categorization. *Behav. Brain Res.* 287, 285–293. doi:10.1016/j.bbr.2015.03.042.

Nagel, I. E., Schumacher, E. H., Goebel, R., and D'Esposito, M. (2008). Functional MRI investigation of verbal selection mechanisms in lateral prefrontal cortex. *Neuroimage* 43, 801–7. doi:10.1016/j.neuroimage.2008.07.017.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., and Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* 53, 695–9. doi:10.1111/j.1532-5415.2005.53221.x.

Nelson, H. E. (1976). A modified card sorting test sensitive to frontal lobe defects. *Cortex A J. Devoted to Study Nerv. Syst. Behav.* 12, 313–324. doi:10.1016/S0010-9452(76)80035-4.

Nelson, D. L., McEvoy, C. L., and Schreiber, T. A. (2004). The University of South Florida free association, rhyme, and word fragment norms. *Behav. Res. Methods, Instruments, Comput.* 36, 402–407. doi:10.3758/BF03195588.

Nichols, T. E., and Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Hum. Brain Mapp.* 15, 1–25. doi:10.1002/hbm.1058.

Nielson, K. A., Douville, K. L., Seidenberg, M., Woodard, J. L., Miller, S. K., Franczak, M., Antuono, P., and Rao, S. M. (2006). Age-related functional recruitment for famous name recognition: An event-related fMRI study. *Neurobiol. Aging* 27, 1494–1504. doi:10.1016/j.neurobiolaging.2005.08.022.

Noonan, K. A., Jefferies, E., Corbett, F., and Lambon Ralph, M. A. (2010). Elucidating the Nature of Deregulated Semantic Cognition in Semantic Aphasia: Evidence for the Roles of Prefrontal and Temporo-parietal Cortices. *J. Cogn. Neurosci.* 22, 1597–1613. doi:10.1162/jocn.2009.21289.

Noonan, K. A., Jefferies, E., Visser, M., and Lambon Ralph, M. A. (2013). Going beyond inferior prefrontal involvement in semantic control: evidence for the additional contribution of dorsal angular gyrus and posterior middle temporal cortex. *J. Cogn. Neurosci.* 25, 1824–50. doi:10.1162/jocn_a_00442.

Noppeney, U., Phillips, J., and Price, C. (2004). The neural areas that control the retrieval and selection of semantics. *Neuropsychologia* 42, 1269–80. doi:10.1016/j.neuropsychologia.2003.12.014.

Oldfield, R.C. (1971). The assessment and analysis of handedness : The Edinburg Inventory. Neuropsychologia 9 : 97-113. doi: 10.1016/0028-3932(71)90067-4

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., and Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. *Psychol. Aging* 17, 299–320. doi:10.1037/0882-7974.17.2.299.

Peelle, J. E., Chandrasekaran, K., Powers, J., Smith, E. E., and Grossman, M. (2013). Age-related vulnerability in the neural systems supporting semantic processing. *Front. Aging Neurosci.* 5, 46. doi:10.3389/fnagi.2013.00046.

Pennequin, V., Fontaine, R., Bonthoux, F., Scheuner, N., and Blaye, A. (2006). Categorization Deficit in Old Age: Reality or Artefact? *J. Adult Dev.* 13, 1–9. doi:10.1007/s10804-006-9000-5.

Petrides, M., and Pandya, D. N. (2002). Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. *Eur. J. Neurosci.* 16, 291–310. doi:10.1046/j.1460-9568.2001.02090.x.

Reitan, R. M. (1955). The relation of the trail making test to organic brain damage. - *J Consult Psychol.* 19, 4. doi:10.1037/h0044509.

Reuter-Lorenz, P. A., and Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Curr. Dir. Psychol. Sci.* 17, 177–182. doi:10.1111/j.1467-8721.2008.00570.x.

Robbins, T., and Roberts, A. (2007). Differential Regulation of Fronto-Executive Function by the Monoamines and Acetylcholine. *Cereb. Cortex* 17, i151–i160. doi:10.1093/cercor/bhm066.

Roskies, A. L., Fiez, J. A., Balota, D. A., Raichle, M. E., and Petersen, S. E. (2001). Task-Dependent Modulation of Regions in the Left Inferior Frontal Cortex during Semantic Processing. *J. Cogn. Neurosci.* 13, 829–843. doi:10.1162/08989290152541485.

Santi, A., Raposo, A., Frade, S., and Marques, J. F. (2016). Concept typicality responses in the semantic memory network. *Neuropsychologia* 93, 167–175. doi:10.1016/j.neuropsychologia.2016.10.012.

Simard, F., Joanette, Y., Petrides, M., Jubault, T., Madjar, C., and Monchi, O. (2011). Fronto-striatal contribution to lexical set-shifting. *Cereb. Cortex* 21, 1084–93. doi:10.1093/cercor/bhq182.

Smith, S. M. (2002). Fast robust automated brain extraction. *Hum. Brain Mapp.* 17, 143–155. doi:10.1002/hbm.10062.

Smith, S., and Nichols, T. (2009). Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage* 44, 83–98. doi:10.1016/j.neuroimage.2008.03.061.

Spreng, R. N., Wojtowicz, M., and Grady, C. L. (2010). Reliable differences in brain activity between young and old adults: A quantitative meta-analysis across multiple cognitive domains. *Neurosci. Biobehav. Rev.* 34, 1178–1194. doi:10.1016/j.neubiorev.2010.01.009.

Springer, M.V., A.R. McIntosh, G. Winocur, and C.L. Grady (2005). The relation between brain activity during memory tasks and years of education in young and older adults. *Neuropsychology*, 19, 181-92.

Steffener, J., Barulli, D., Habeck, C., and Stern, Y. (2014). Neuroimaging explanations of age-related differences in task performance. *Front. Aging Neurosci.* 6, 1–10. doi:10.3389/fnagi.2014.00046.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *J. Int. Neuropsychol. Soc.* 8, 448–460. doi:10.1017/S1355617702813248.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia* 47, 2015–28. doi:10.1016/j.neuropsychologia.2009.03.004.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *J. Exp. Psychol.* 18, 643–662. doi:10.1037/h0054651.

Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., and Farah, M. J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a reevaluation. *Proc. Natl. Acad. Sci. U. S. A.* 94, 14792–7.

Tombaugh, T. (1999). Normative Data Stratified by Age and Education for Two Measures of Verbal Fluency FAS and Animal Naming. *Arch. Clin. Neuropsychol.* 14, 167–177. doi:10.1016/S0887-6177(97)00095-4.

Verhaegen, C., and Poncelet, M. (2013). Changes in naming and semantic abilities with aging from 50 to 90 years. *J. Int. Neuropsychol. Soc.* 19, 119–26. doi:10.1017/S1355617712001178.

Wagner, A. D., Maril, A., Bjork, R. A., and Schacter, D. L. (2001). Prefrontal Contributions to Executive Control: fMRI Evidence for Functional Distinctions within Lateral Prefrontal Cortex. *Neuroimage* 14, 1337–1347. doi:10.1006/nimg.2001.0936.

Wang, X., Tao, Y., Tempel, T., Xu, Y., Li, S., Tian, Y., and Li, H. (2016). Categorization Method Affects the Typicality Effect: ERP Evidence from a Category-Inference Task. *Front. Psychol.* 7. doi:10.3389/fpsyg.2016.00184.

Wechsler, D. (1981). WAIS-R manual. The psychological corporation. *New York.*

Wierenga, C. E., Benjamin, M., Gopinath, K., Perlstein, W. M., Leonard, C. M., Rothi, L. J. G., Conway, T., Cato, M. A., Briggs, R., and Crosson, B. (2008). Age-related changes in word retrieval: Role of bilateral frontal and subcortical networks. *Neurobiol. Aging* 29, 436–451. doi:10.1016/j.neurobiolaging.2006.10.024.

Wingfield, A., and E. A. L. Stine-Morrow. 2000. Language and speech. The handbook of aging and cognition, ed. by F. I.M.Craik, and T. A. Salthouse, 359–416.Mahwah, NJ: Lawrence Erlbaum Associates.

Wingfield, A., and Grossman, M. (2006). Language and the aging brain: patterns of neural compensation revealed by functional brain imaging. *J. Neurophysiol.* 96, 2830–9. doi:10.1152/jn.00628.2006.

Whitney, C., Grossman, M., and Kircher, T. T. J. (2009). The influence of multiple primes on bottom-up and top-down regulation during meaning retrieval: evidence for 2 distinct neural networks. *Cereb. Cortex* 19, 2548–60. doi:10.1093/cercor/bhp007.

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M. A., and Jefferies, E. (2011). The Neural Organization of Semantic Control: TMS Evidence for a Distributed Network in Left Inferior Frontal and Posterior Middle Temporal Gyrus. *Cereb. Cortex* 21, 1066–1075. doi:10.1093/cercor/bhq180.

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M. a, and Jefferies, E. (2012). Executive semantic processing is underpinned by a large-scale neural network: revealing the contribution of left prefrontal, posterior temporal, and parietal cortex to controlled retrieval and selection using TMS. *J. Cogn. Neurosci.* 24, 133–47. doi:10.1162/jocn_a_001

Table 1: Means (M) and standard deviations (SD) of the demographic and neuropsychological variables of all participants (n=40).

	Younger (n = 20)	**Older (n = 20)**		
	M (SD)	M (SD)	F (1.38)	*p-values*
Age	24.85 (3.85)	69.45 (4.54)	1129.02	< 0.001
Gender (F: M)	16:4	17:3	0.603	0.714
Education (years)	17.95 (2.52)	18.85 (2.88)	1.01	0.301
Edinburgh inventory	95%	96%	0.89	0.122
MoCA	28.6 (1.53)	28.7 (1.03)	0.058	0.81
Stroop C (seconds)	49.95 (6.88)	62.2 (9.12)	22.95	< 0.001
Stroop W (seconds)	39.25 (4.02)	45.30 (5.82)	14.61	< 0.001
Stroop C–W (seconds)	83.05 (13.42)	114.65 (22.29)	29.5	< 0.001
TMT A (seconds)	17.40 (4.35)	27.60 (8.22)	23.98	< 0.001
TMT B (seconds)	41.60 (11.77)	62.82 (16.29)	22.24	< 0.001
TMT B-A (seconds)	24.20 (2.5)	34.90 (3.53)	6.08	<.05
Digits forward	10.5 (1.67)	9.65 (1.75)	2.46	0.125
Digits backward	8.45 (2.03)	6.8 (1.73)	7.6	< 0.01
Brixton (errors)	1.15 (1.03)	1.45 (1.05)	0.82	0.37
WCST (errors)	0.88 (1.19)	1.05 (1.27)	0.41	0.527
Semantic Fluency (2 minutes)	39.70 (8.27)	28.85 (8.1)	17.55	< 0.001

MoCA: Montreal Cognitive Assessment; Stroop-C: Stroop-Color; Stroop-W: Stroop-Word; TMT A & B: Trail Making Test A & B; WCST: Wisconsin Card Sorting Test
SD: standard deviation

Table 2: Behavioral performance (response times and correct responses) during rule repetition in word-matching task.

	Younger (n=20)	**Older (n=20)**		
	Mean (SD)	Mean (SD)	F(1.38)	*p-values*
Response times (in milliseconds)				
Functional	1669 (390)	2234 (467)	17.18	< 0.001
Typical	2366 (755)	2888 (490)	6.70	< 0.05
Atypical	2559 (949)	3103 (549)	4.90	< 0.05
Correct responses (in %)				
Functional	97.25 (2.60)	94.40 (3.75)	3.26	0.08
Typical	96.09 (2.20)	93.30 (4.25)	3.71	0.061
Atypical	95.32 (3.51)	91.48 (4.30)	15.18	< 0.001

SD: standard deviation

Table 3: Significant activation clusters associated with the repetition of semantic rules (functional, typical, atypical) for all age groups.

Cluster region	Cluster size	t-value	MNI coordinates (x, y, z)		
Functional > control					
Right cerebellum	594706	12.3	9	-75	-28
Left insula cortex (area 13)	-	12.1	-31	21	-1
Left inferior parietal cortex (area 39, AG)	-	12.1	-31	21	-1
Right insula cortex (area 13)	-	11.9	32	25	1
Right occipital cortex (area 17)	-	11.1	15	-91	1
Left occipital cortex (area 17)	-	11.1	-13	-91	-4
Right inferior parietal cortex (area 39, AG)	-	9.51	35	-62	42
Right dorsal medial PFC (area 8)	-	9.48	35	-62	42
Left posterior PFC (area 44)	-	9.36	-44	17	25
Right mid-dorsolateral PFC (area 9)	-	9.02	49	35	25
Left inferior temporal cortex (area 37 FG)	-	8.48	-48	-56	-14
Left cerebellum	-	7.25	-25	-62	-31

Left dorsolateral PFC (area 46)	-	6.77	-50	44	12
Left posterior middle temporal cortex (area 21)	-	6.53	-52	-35	2
Right superior parietal cortex (area 7)	-	6.49	11	-74	57
Right thalamus	-	6.3	9	-3	1
Left orbitofrontal cortex (area 11)	-	5.64	-21	39	-22
Right lateral premotor cortex (area 6)	-	5.11	36	-2	39
Right frontopolar cortex (area 10)	-	4.99	37	53	24
Right caudate nucleus	-	4.24	19	-14	22
Left ventrolateral PFC (area 47)	-	4.18	-54	26	-5
Left putamen	-	3.54	-17	-2	-1
Left frontopolar (area 10)	-	2.94	-35	62	-9
Right posterior middle temporal cortex (area 21)	551	4.33	66	-31	-12
Typical > control					
Left insula cortex (area 13)	640006	14.8	-31	21	-1
Left occipital cortex (area 18)	-	14.6	-13	-94	-4
Right cerebellum	-	13.9	8	-76	-27

Left inferior parietal cortex (area 39, AG)	-	13.1	-28	-66	41
Right insula cortex (area 13)	-	13.1	32	24	1
Left posterior PFC (area 44)	-	12.5	-39	23	23
Right occipital cortex (area 18)	-	11.4	20	-93	-1
Right inferior parietal cortex (area 39, AG)	-	10.9	34	-62	42
Left cerebellum	-	10.5	-39	-67	-29
Right dorsolateral PFC (area 9/46)	-	9.96	51	31	28
Left lateral premotor cortex (area 6)	-	9.86	-36	1	34
Left inferior temporal cortex (area 37 FG)	-	9.48	-48	-49	-14
Left dorsolateral PFC (area 46)	-	7.99	-48	47	1
Right superior parietal cortex (area 7)	-	7.4	12	-75	57
Left orbitofrontal cortex (area 11)	-	6.5	-21	-77	14
Right lateral premotor cortex (area 6)	-	6.16	35	4	58
Right frontopolar cortex (area 10)	-	5.62	24	48	-15
Left globus pallidus	-	5.06	-17	-3	-3
Left superior temporal cortex (area 22)	-	4.93	-57	-37	6

Left frontopolar cortex (area 10)	-	4.93	-37	54	24
Left dorsal medial PFC (area 8)	-	4.28	31	13	34
Left ventrolateral PFC (area 47)	-	4.08	-25	22	-26
Right dorsal medial PFC (area 8)	-	3.04	-34	33	48
Atypical > control					
Left insula cortex (area 13)	728734	15.5	-29	22	0
Right insula cortex (area 13)	-	15.1	32	25	1
Right dorsal medial PFC (area 8)	-	14.1	5	26	44
Right cerebellum	-	13.6	9	-77	-27
Left inferior parietal cortex (area 39, AG)	-	13.5	-28	-66	42
Left occipital cortex (area 18)	-	13.4	-13	-94	-3
Left posterior PFC (area 44)	-	12.9	-39	23	23
Right inferior parietal cortex (area 39, AG)	-	12.1	33	-61	45
Right occipital cortex (area 18)	-	11.9	20	-94	-2
Left cerebellum	-	11	37	-66	-28
Right mid-dorsolateral PFC (area 9)	-	10.8	53	36	24

Left lateral premotor cortex (area 6)	-	9.94	-35	0	34
Right posterior cingulate cortex (area 23)	-	9	29	-63	10
Left frontopolar cortex (area 10)	-	8.39	-45	54	1
Right superior parietal cortex (area 7)	-	8.27	12	-75	58
Left inferior temporal cortex (area 37, FG)	-	8.17	-48	-49	-13
Right globus pallidus	-	7.66	15	0	-2
Right lateral premotor cortex (area 6)	-	6.88	33	4	54
Right posterior PFC (area 44)	-	6.76	41	13	26
Left orbitofrontal cortex (area 11)	-	6.05	-21	49	-16
Right inferior parietal cortex (area 40, SM)	-	5.83	48	-41	46
Right frontopolar cortex (area 10)	-	5.72	24	47	-16
Left thalamus	-	5.55	-20	-33	4
Right caudate nucleus	-	5.45	19	-12	22
Right posterior middle temporal cortex (area 21)	-	4.75	54	-40	-8
Left globus pallidus	-	4.51	-17	-4	-3
Left superior parietal cortex (area 7)	-	4.18	-12	-72	62

Left ventrolateral PFC (area 45)	-	3.42	-53	20	-2

AG: angular gyrus; PFC: prefrontal cortex; FG: fusiform gyrus; SM: supramarginal gyrus.

Table 4: Significant activation clusters associated to repetition of functional rule relative to control condition for older minus younger adults.

Cluster region	Cluster size	t-value	MNI coordinates (x, y, z)		
Right frontopolar cortex (area 10)	4000	4.49	2	62	-11
Left orbitofrontal cortex (area 11)	-	4.3	-16	37	-10
Right ventrolateral PFC	349	5.31	25	19	-22
Left frontopolar cortex (area 10)	145	3.85	-3	66	6

PFC: prefrontal cortex

Table 5: Significant activation clusters associated to repetition of typical rule relative to control condition for older minus younger adults.

Cluster region	Cluster size	t-value	MNI coordinates (x, y, z)		
Right frontopolar cortex (area 10)	96794	5.42	5	53	-8
Left frontopolar cortex (area 10)	-	5.33	-10	62	23
Left orbitofrontal cortex (area 11)	-	4.98	-7	32	-16
Right ventrolateral PFC (area 47)	-	4.44	39	31	-20
Left dorsolateral PFC (area 46)	-	4.25	-55	38	6
Right orbitofrontal cortex (area 11)	-	3.9	16	20	-19
Left ventrolateral PFC (area 47)	-	3.8	-33	20	-20
Right dorsal medial PFC (area 8)	-	3.12	41	19	41

Right lateral premotor cortex (area 6)	93147	5.29	21	-8	57
Left superior parietal cortex (area 7)	-	5.17	-25	-64	69
Left precentral (area 4)	-	5.07	-21	-16	63
Left inferior parietal cortex (area 39, AG)	-	4.86	-40	-71	38
Left anterior cingulate cortex (area 24)	-	4.62	-1	-8	45
Left inferior parietal cortex (area 40, SM)	-	4.17	-60	-36	40
Left posterior cingulate cortex (area 23)	-	2.44	-12	-29	36
Right occipital cortex (area 18)	1582	4.14	37	-82	20

AG: angular gyrus; PFC: prefrontal cortex; SM: supramarginal gyrus.

Table 6: Significant activation clusters associated to repetition of atypical rule relative to control condition for older minus younger adults.

Cluster region	Cluster size	t-value	MNI coordinates (x, y, z)		
Right frontopolar cortex (area 10)	49815	5.39	0	57	-2
Left frontopolar cortex (area 10)	-	5.32	-10	62	23
Left dorsal medial PFC (area 8)	-	5.28	-26	38	48
Right dorsal medial PFC (area 8)	-	4.97	5	51	45
Right ventrolateral PFC (area 47)	-	4.87	40	32	-21
Left orbitofrontal cortex (area 11)	-	4.56	-7	32	-15
Right orbitofrontal cortex (area 11)	-	4.1	17	20	-20
Left lateral premotor cortex (area 6)	16275	4.9	-19	-20	63
Left ventrolateral PFC (area 45)	8908	5.1	-55	39	-5
Right posterior cingulate cortex (area 31)	3825	4.54	1	-26	47
Right lateral premotor cortex (area 6)	1747	5.7	21	-8	58
Left superior parietal cortex (area 7)	346	4.11	-22	-61	69

Left inferior parietal cortex (area 39, AG)	327	4.49	-40	-71	38

AG: angular gyrus; PFC: prefrontal cortex

Table 7: Significant activation clusters associated to repetition of functional rule relative to typical rule

Cluster region	Cluster size	t-value	MNI coordinates (x, y, z)		
Left frontopolar cortex (area 10)	264446	10.3	-4	59	-1
Left inferior parietal cortex (area 40, SM)	-	8.04	-59	-38	38
Left superior temporal cortex (area 22)	-	7.57	-59	-4	-9
Left inferior parietal cortex (area 39, AG)	-	6.76	-49	-63	23
Right posterior cingulate (area 31)	-	6.66	8	-24	41
Left temporopolar cortex (area 38)	-	6.43	-45	18	-31
Right orbitofrontal cortex (area 11)	-	6.43	9	35	-7
Left insula cortex (area 13)	-	6.22	-34	5	8
Left anterior cingulate cortex (area 32)	-	5.86	-2	7	37
Left superior parietal cortex (area 7)	-	5.05	-24	-44	75
Left mid-dorsolateral PFC (area 9)	-	4.38	-23	28	33

Right mid-dorsolateral PFC (area 9)	-	4.08	17	52	28
Left lateral premotor cortex (area 6)	-	3.88	-8	-10	60
Left dorsal medial PFC (area 8)	-	3.73	-12	48	48
Left superior temporal cortex (area 22)	-	3.23	-67	-38	14
Left posterior middle temporal cortex (area 21)	-	2.65	-49	-37	-2
Right inferior parietal cortex (area 40, SM)	137227	7.8	60	-32	31
Right temporopolar cortex (area 38)	-	6.85	51	20	-26
Right inferior parietal cortex (area 39, dorsal AG)	-	6.5	57	-55	12

AG: angular gyrus; PFC: prefrontal cortex; SM: supramarginal gyrus.

Table 8: Significant activation clusters associated to repetition of atypical rule relative to typical.

Cluster region	Cluster size	t-value	MNI coordinates (x, y, z)		
Right dorsal medial PFC (area 8)	525803	8.08	29	25	37
Right inferior parietal cortex (area 39, AG)	-	5.08	54	-60	32
Right inferior parietal cortex (area 40, SM)	-	5.61	61	-34	51
Right posterior cingulate (area 31)	-	5.47	11	-50	42
Right mid-dorsolateral PFC (area 9)	-	5.43	44	41	29
Right superior parietal cortex (area 7)	-	5.34	2	-71	63
Left inferior parietal cortex (area 40, SM)	-	5.12	-58	-43	43
Left anterior cingulate (area 23)	-	4.92	5	-7	41
Right putamen	-	4.9	28	11	-8
Left mid-dorsolateral cortex (area 9)	-	4.84	-32	36	35
Right superior temporal cortex (area 22)	-	4.84	55	-13	-9

Left inferior parietal cortex (area 39, AG)	-	4.8	-57	-56	21
Left frontopolar cortex (area 10)	-	4.79	-20	59	21
Right cerebellum	-	4.75	32	-79	-29
Left lateral premotor cortex (area 6)	-	4.58	-16	11	59
Right thalamus	-	4.43	9	-3	3
Right superior frontal cortex (area 6/8)	-	4.36	9	19	53
Right inferior temporal (area 37)	-	4.36	48	-57	-20
Right lateral premotor cortex (area 6)	-	4.27	31	9	65
Right postcentral (area 4)	-	4.18	25	-25	75
Right inferior temporal cortex (area 20)	-	3.94	42	-1	-39
Right frontopolar (area 10)	-	3.77	6	54	16
Right occipital cortex (area 19)	-	3.75	38	-86	15
Left cerebellum	-	3.61	-29	-60	-35
Right posterior PFC (area 44)	-	3.41	56	19	10

AG: angular gyrus; PFC: prefrontal cortex; SM: supramarginal gyrus.

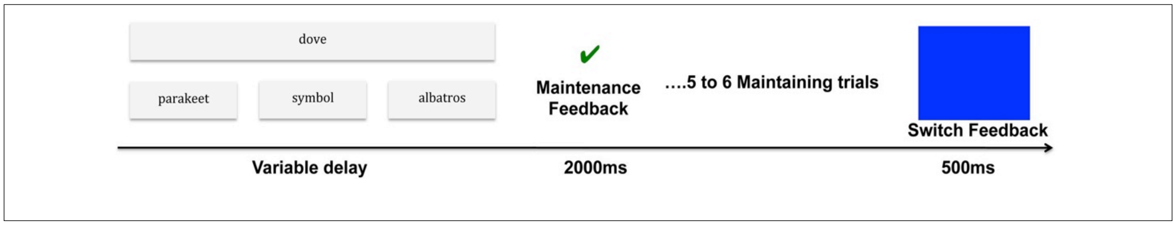

Figure 1. Experimental procedure of the word-matching task. In this example, each participant performed a task in which a target word presented at the top of the screen, dove (‘*colombe*’) had to be paired with one of three reference words, presented at the bottom, according to three possible semantic relationships: (a) typically related word (co-hyponyms) parakeet (‘*perruche*’); (b) atypically related word (co-hyponyms) albatross (‘*albatros*’); and (c) functionally related words (F) symbol (‘*symbole*’). The sorting period was followed by a maintenance feedback signal (green checkmark displayed for 2000 ms) indicating that participants should repeat the application of the same semantic rule as in the previous trial. After 5 or 6 correct same rule application trials, the rule changed (blue screen displayed for 500 ms) and participants had to discover the new classification rule and maintain it.

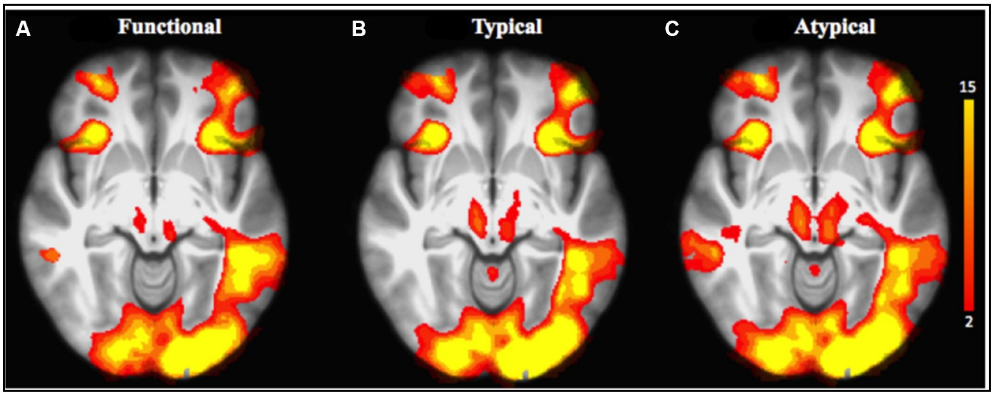

Figure 2. Brain activation related to the repetition of the application of the functional rule (cf. right), typical rule (cf. middle) and atypical rule (cf. left) relative to control condition for all age groups. The scale illustrated the value of the t-maps. Threshold-free Cluster Enhancement (TFCE) at p<.05.

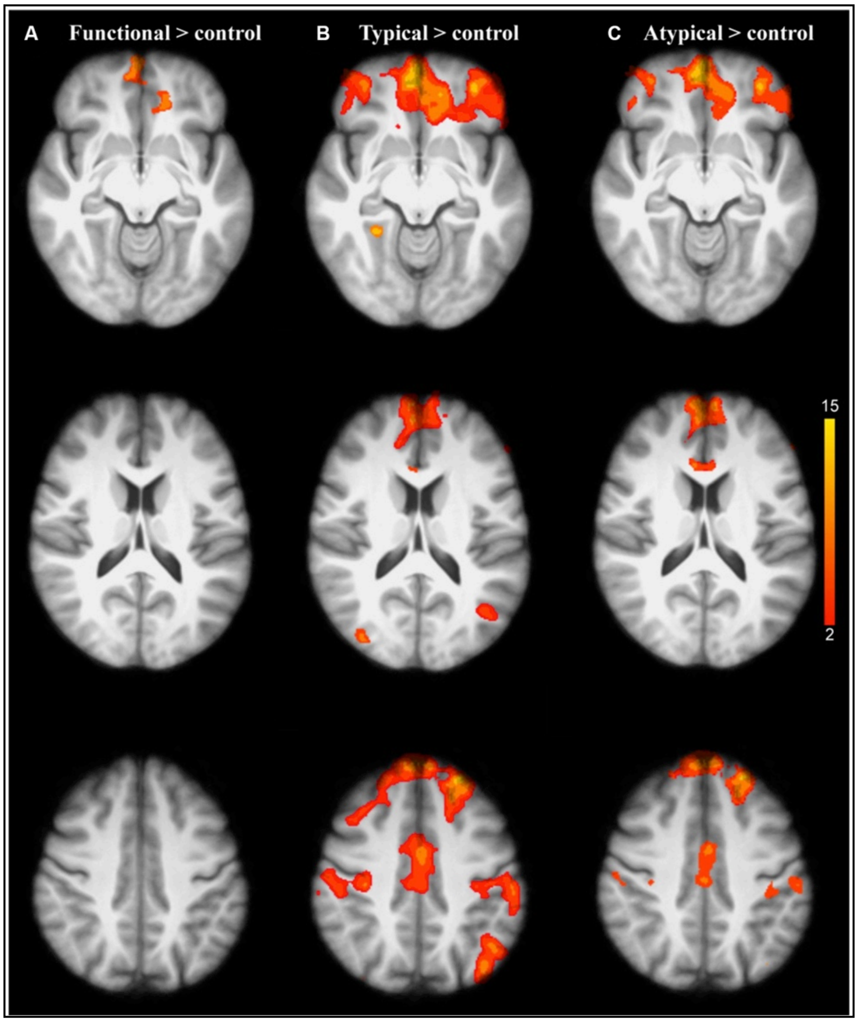

Figure 3. Brain activation related to the repetition of each semantic rule relative to control condition for older adults compared to the younger adults: (A) Functional; (B) Typical; (C) Atypical. The scale illustrated the value of the t-maps. Threshold-free Cluster Enhancement (TFCE) at $p<.05$.

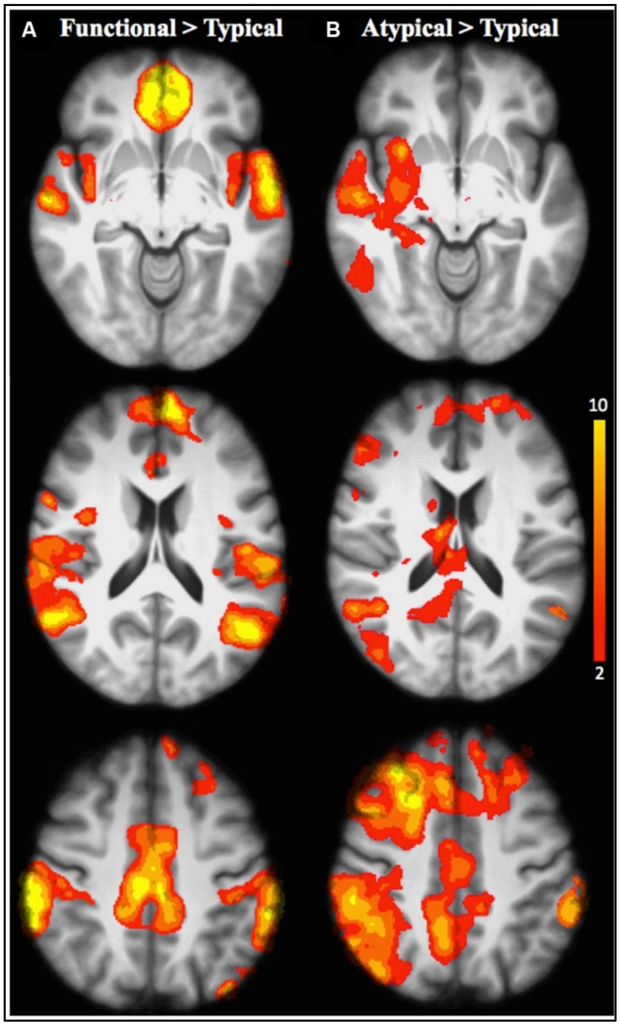

Figure 4. Brain activation for the inter-semantic rules comparison in all age groups: (A) Functional relative to Typical rule; (B) Atypical relative to Typical rule. The scale illustrated the value of the t-maps. Threshold-free Cluster Enhancement (TFCE) at p<.05.

CHAPITRE VI : DISCUSSION ET CONCLUSION GÉNÉRALE

6.1 Rappel des objectifs et synthèse des principaux résultats

Ce travail de thèse avait pour objectif d'examiner, à l'aide de la neuroimagerie fonctionnelle, l'évolution des changements de l'activité cérébrale associée aux aspects exécutifs du traitement sémantique des mots au cours du vieillissement sain. ***Par le biais de trois études*** intégrant une approche neurofonctionnelle et comportementale, les résultats permettent d'apporter une perspective nouvelle sur les mécanismes de la réorganisation neurofonctionnelle observés au cours du vieillissement, en caractérisant la diversité des adaptations neurofonctionnelles manifestées par l'adulte âgé destinées au maintien de la performance du traitement sémantique des mots. ***La première étude*** avait pour objectif d'analyser les corrélats neurofonctionnels des différences d'âge associés aux processus exécutifs de maintien (stratégie d'exploitation du savoir ou *clustering*) et de changement (stratégie d'exploration d'autres connaissances lorsque les premières s'épuisent, ou *switching*) dans une tâche de fluence verbale (sémantique et orthographique), réalisée sous un mode *expressif et auto-rythmé*. L'utilisation d'un design d'IRMf mixte novateur permet, pour la première fois, de mieux caractériser la signification fonctionnelle de la réorganisation cérébrale observée au cours du vieillissement lors de la mise en jeu des processus stratégiques[4] « auto-initiés » de regroupement et de changement qui sont à même de déterminer l'efficience en fluence verbale. Les résultats montrent, qu'en dépit d'une performance équivalente (en termes de nombre total de mots

---

[4] La capacité à maintenir une règle de regroupement de mots appartenant à une même sous-catégorie définit la stratégie de regroupement (ou *d'exploitation* du savoir) alors que la capacité à changer de stratégie pour passer d'une sous-catégorie à une autre définit la stratégie *de changement* (ou *d'exploration* d'autres connaissances lorsque les premiers s'épuisent. Dans le cadre de ce travail de thèse, une certaine terminologie sera privilégiée dépendamment de la nature de la tâche utilisée Pour la tâche de fluence verbale (étude 1), ce sera stratégie de regroupement et stratégie de changement. Pour la tâche de catégorisation sémantique (études 2 et 3), ce sera la capacité de maintien et changement

produits) entre les adultes âgés performants et les adultes jeunes en fluence sémantique et orthographique, une différence entre les deux groupes apparait dans l'utilisation de la stratégie de regroupement et ce, particulièrement en fluence sémantique plutôt qu'orthographique. Cette différence est d'ailleurs accompagnée d'une diversité des manifestations neurofonctionnelles dépendamment de la nature de la tâche (sémantique ou orthographique) et du processus exécutif engagé (maintien ou changement). *Les principaux résultats neurofonctionnels de cette première étude* montrent la présence d'une activation du cortex temporal inférieur latéralisée à gauche chez les adultes jeunes alors que les adultes âgés présentent une activité temporale bilatérale et relativement symétrique et ce, lors de la mise en jeu de la stratégie de regroupement en fluence sémantique. De plus, l'analyse de corrélation entre la stratégie de regroupement sémantique et le changement de l'activité cérébrale dans les deux groupes d'âge, révèle une implication spécifique du cortex temporal inférieur gauche chez les adultes âgés et du cortex frontal postérieur gauche et le noyau caudé gauche chez les adultes jeunes. Cependant, lors de la mise en jeu de la stratégie de changement entre différentes sous-catégories en fluence orthographique, des modifications dans les patrons d'activité préfrontale apparaissent chez l'adulte âgé dont la performance cognitive est comparable à celle des adultes jeunes et ce, en termes du nombre total de mots produits et des processus stratégiques. Ainsi, relativement à une bilatéralisation préfrontale présente chez les adultes âgés, les adultes jeunes montrent un patron d'activation comparable mais latéralisé plus à gauche. En somme, la correspondance entre les données neurofonctionnelles et comportementales dans la présente étude est particulièrement intéressante puisqu'elle révèle une différence dans les mécanismes de la réorganisation neurofonctionnelle entre adultes âgés et jeunes, qui concerne davantage les processus stratégiques. Une telle différence n'a jusqu'à ce jour jamais été rapportée par les études IRMf principalement focalisées sur la différence quantitative définie en termes de nombre total de mots produits entre les deux groupes d'âge.

Dans un second travail, les *deux dernières études (études 2 et 3)* ont été conduites avec des objectifs distincts au moyen d'une tâche de catégorisation sémantique. ***La deuxième étude*** avait pour objectif d'examiner des différences d'âge dans les mécanismes de réorganisation neurofonctionnelle associés à la capacité à maintenir ou à changer l'utilisation d'un lien sémantique (associé, typique ou atypique) sur la base *de feedbacks* de l'expérimentateur. Ce faisant, nous avons également cherché à explorer l'existence des liens éventuels, entre les modifications de l'activité cérébrale dans le groupe d'adultes âgés et les caractéristiques de son profil de performance dans des épreuves évaluant différents processus du contrôle exécutif (maintien/mise à jour, flexibilité, inhibition). Enfin, ***la troisième étude*** a permis d'appréhender la différence d'âge dans les corrélats neurofonctionnels sous-jacents au processus de maintien d'un lien sémantique spécifique (associé, typique ou atypique) et ce, de nature à rendre compte de la variabilité des manifestions neurofonctionnelles selon le degré de contrôle requis par le traitement sémantique. *Les résultats principaux correspondant aux études 2 et 3* montrent une diversité des adaptations neurofonctionnelles augurant favorablement une efficience des aspects exécutifs du traitement sémantique des mots au cours du vieillissement. Plus spécifiquement, les résultats comportementaux et neurofonctionnels de l'étude 2 montrent, qu'en dépit d'une performance comportementale comparable entre les deux groupes d'âge, les adultes âgés sollicitent un patron d'activité cérébrale différent de celui des adultes jeunes, caractérisé par un déplacement de l'activation cérébrale vers les régions pariétales inférieures alors que des activations préfrontales inférieures sont présentes chez les adultes jeunes. Ces modifications neurofonctionnelles illustrent la présence d'un mécanisme de réorganisation cérébrale spécifique au vieillissement, opérant au delà des régions frontales classiquement dévolues aux ressources exécutives. Le recours aux régions pariétales inférieures suggère l'efficience du système exécutif impliqué dans le traitement sémantique des mots au cours du vieillissement. Les analyses corrélationnelles entre le changement de l'activation pariétale inférieure (BA 39/40) et les mesures comportementales montrent une corrélation positive pour les adultes âgés et négative pour les adultes jeunes avec la précision des réponses alors qu'un profil inverse est observé avec le temps de réponse. À travers une étude exploratoire conduite au sein du groupe d'adultes âgés, l'exploration du lien entre les activations au niveau des régions fronto-pariétales et la variabilité présumée du profil de performance aux épreuves exécutives a révélé des résultats prometteurs. La présence de deux profils exécutifs clairement distincts a été observée parmi le groupe d'adultes âgés. Chez le sous-groupe avec des performances élevées aux épreuves associées au processus de flexibilité cognitive (*switching-profile*), une corrélation positive est observée entre la précision des réponses et le changement de l'activité cérébrale du cortex pariétal inférieur gauche (BA39/40) et négative avec le cortex dorso-latéral préfrontal gauche (BA 9/46). Le sous-groupe d'adultes âgés avec des performances élevées aux épreuves associées au processus de maintien/mise à jour *(updating-profile)* montre un patron d'activation inverse. Cet ensemble de résultats révèle des mécanismes de réorganisation neurofonctionnelle influencée par l'âge mais également par les caractéristiques du profil exécutif. Enfin, dans le cadre de ce second travail, la troisième étude a démontré tout d'abord un changement de la performance comportementale et de l'activité cérébrale en fonction du degré du contrôle requis par le maintien d'un lien sémantique (associé < typique < atypique) et ce, indépendamment de l'âge. Toutefois, la comparaison de groupe a montré des différences neurofonctionnelles au niveau du cortex dorso-latéral préfrontal avec une augmentation de la bilatéralisation préfrontale pour des liens sémantiques nécessitant un degré de contrôle plus élevé (une activité est plus diffuse lors du maintien d'un lien atypique). Un tel profil de résultat met en évidence des mécanismes adaptatifs de réorganisation neurofonctionnelle au niveau des régions préfrontales traduisant ainsi un déploiement graduel des ressources neurofonctionnelles en fonction du niveau de contrôle requis par la tâche. Autrement dit, pour répondre efficacement aux exigences d'un traitement cognitif plus couteux, les adultes âgés tendent à engager de manière plus accrue et diffuse les ressources neurofonctionnelles nécessaires, à un moment où la contrainte de leur mise en jeu constitue un avantage indéniable.

À la lumière de l'ensemble de nos résultats comportementaux et neurofonctionnels observés dans deux tâches langagières de haut niveau, que sont la fluence verbale et la catégorisation sémantique de mots, les sections subséquentes vont tenter de les confronter à certains travaux ayant rapporté des observations contradictoires de même que ceux qui ouvrent une piste intéressante quant à la nature même du caractère adaptatif du cerveau âgé dans le maintien des habiletés lexico-sémantiques, notion défendue dans notre travail.

6.2 Maintien des habiletés de production orale de mots au cours du vieillissement : Une question de compromis entre gains et pertes ?

La notion de compromis n'est pas méconnue des études sur le vieillissement. Dans un article intitulé '*How ageing is shaped by trade-offs' d'*Annette Baudisch (2009), l'idée directrice repose sur le fait qu'une compréhension du vieillissement demeure très partielle sans la compréhension des mécanismes de compromis entre pertes et gains. De plus, cette centration sur la notion du compromis conduit l'auteur vers une conception des mécanismes adaptatifs associées à l'âge comme des phénomènes qui ne sont pas dévolus aux pertes cognitives mais seraient également liés aux gains, preuve d'une réciprocité mécanistique spécifique au vieillissement. Une telle perspective du vieillissement s'aligne d'ailleurs avec les modèles neurocognitifs actuels du vieillissement qui viennent asseoir leurs conclusions dans la continuité des positions théoriques classiques prises en considération par la psychologie cognitive du vieillissement. D'ailleurs, selon le modèle de Craik et Bialystok (2006, 2008), la prise en compte des connaissances sémantiques et du contrôle exécutif comme deux composantes interdépendantes est susceptible d'expliquer la complexité des changements cognitifs spécifiques au vieillissement et d'en révéler la contribution en tant que ressources adaptatives augurant favorablement le maintien de la performance avec l'âge. En effet, même si l'adulte âgé est de plus en plus confronté à des limites touchant certains domaines de la cognition, il serait néanmoins capable d'augmenter ses ressources dans d'autres domaines, sur la base des connaissances acquises tout au long de la vie et de développer une expertise dont résultera des adaptations et des réorganisations stratégiques.

En ce sens, un ensemble d'études comportementales et neurofonctionnelles portant sur la tâche de fluence verbale (Chouiter et al., 2016 ; Hughes & Bryan, 2002 ; Hurks et al., 2010 ; Mayr & Kliegl, 2000 ; Unsworth, Spillers, & Brewer, 2011) ont rapporté des résultats parfois contradictoires dépendamment des paramètres de la tâche utilisée (mode et durée d'évocation lexicale) ou les caractéristiques des adultes âgés (niveau de scolarité, âge) et ce au-delà de l'intégrité du stock lexico-sémantique dont est tributaire l'efficience en fluence verbale. *D'un point de vue comportemental*, l'analyse quantitative des mots produits délaissée au profit d'une analyse qualitative a permis de distinguer des processus stratégiques de regroupement et de changement et une différence d'âge dans leur mise en jeu et ce, en dépit d'une performance comparable en termes du nombre total de mots produits entre les adultes jeunes et âgés (Hurks et al., 2010; Sauzéon, Raboutet, Rodrigues et al., 2011; Troyer, Moscovitch and Winocur, 1997).

Pour un niveau de performance équivalent entre les adultes jeunes et âgés, les auteurs ont ainsi montré une réorganisation stratégique signe d'une adaptation du fonctionnement cognitif avec l'âge, en réponse à la demande plus coûteuse en ressources requises lors de la mise en jeu du processus stratégique de changement. Toutefois, ce profil comportemental en production de mots soulève la question de savoir si ces adaptations stratégiques - dites spontanées - associées à l'âge trouveraient leurs corollaires dans les réflexions actuelles sur les phénomènes de réorganisation neurofonctionnelle en neurosciences cognitives du vieillissement. *D'un point de vue neurofonctionnel*, un nombre très limité d'études IRMf reposant sur l'utilisation de la fluence verbale ont été réalisées auprès d'une population âgée. Sur la base de méthodologies bien distinctes, ces travaux ont examiné les différences des patrons d'activité cérébrale entre les adultes âgés et les adultes jeunes. L'utilisation d'une tâche de fluence verbale sémantique et orthographique sous un mode rythmé par l'expérimentateur (Meinzer et al., 2009) et une tâche de fluence sémantique explicite et auto-rythmée durant des blocs de production très courts (Nagels et al., 2012) ont conduit à des conclusions partiellement convergentes avec celles retenues dans notre étude sur la fluence verbale. D'ailleurs, les deux études ont exploré l'implication des régions frontales et temporales dans le maintien relatif de la performance en fluence verbale par le biais d'analyse corrélationnelle entre activité cérébrale et nombre total de mots produits par chaque groupe d'âge. Dans l'ensemble, la contribution bilatérale des régions frontales par les adultes âgés ne présenterait pas d'avantage comportemental en fluence sémantique (Meinzer et al., 2009, 2012), de même que pour les régions temporales (Nagels et al., 2012). Cette bilatéralisation frontale liée à l'âge très souvent considérée comme reflétant un phénomène neurofonctionnel bénéfique pour la performance cognitive semble ne pas rendre compte des différences dans les processus stratégiques impliquées, que seule la mise en relation entre réorganisation neurofonctionnelle et cognitive peut distinguer. À notre connaissance, notre étude IRMf sur la fluence verbale est la première à proposer certaines clarifications sur la signification neurofonctionnelle de la réorganisation cérébrale observée chez l'adulte âgé à la suite d'adaptations stratégiques. En effet, la réorganisation cognitive et neuronale observée chez l'adulte âgé suppose qu'un maintien de performance en fluence verbale est déterminé essentiellement par la capacité à recruter des ressources exécutives ou sémantiques dépendamment des exigences de la tâche. D'ailleurs, nos résultats comportementaux et neurofonctionnels lors de la fluence sémantique indiquent que les adultes âgés ont davantage recours aux régions temporales dont relève la stratégie de regroupement basée sur les gains cognitifs (connaissances sémantiques). Or, lorsqu'ils se retrouvent en condition de fluence orthographique, durant laquelle l'usage de la stratégie de changement est plus avantageux pour la performance comparativement à la stratégie de regroupement, les adultes âgés sollicitent les régions frontales et ce, bilatéralement pour soutenir la stratégie de changement qui a pour désavantage d'être plus coûteuse en termes de ressources mais favorable pour une exploration optimale du savoir. Enfin, l'observation de ces mécanismes de réorganisation cognitive et neurofonctionnelle associés à l'âge revêt en outre l'intérêt de concevoir le vieillissement neurocognitif en termes de compromis cognitif, adaptatif et évolutif par lequel la balance entre les gains et pertes est déterminante pour le maintien d'un fonctionnement cognitif optimal proportionnel aux ressources disponibles avec l'avancée en âge. Cette perspective du vieillissement neurocognitif est concordante avec le principe de l'économie du système de traitement de Navon & Gopher (1979) selon lequel l'allocation des ressources nécessaires à la réalisation d'une tâche cognitive dépend de la capacité d'un système de traitement cognitif à maximiser son utilité selon les demandes de la tâche, et des caractéristiques du sujet. Dans le même ordre d'idées, cette réalité fonctionnelle qui s'objective par des réorganisations stratégiques adaptatives spécifiques à un domaine d'expertise est en adéquation avec l'hypothèse de préservation sélective de Krampe & Ericsson, (1996) et l'hypothèse sur l'adaptabilité stratégique de Schunn & Reder, (2001).

À l'heure actuelle, la majorité des modèles neurocognitifs développés pour expliquer les mécanismes de réorganisation neurofonctionnelle sous-jacents au maintien de la performance cognitive au cours du vieillissement font soit l'hypothèse d'une adoption de stratégies différentes soit l'hypothèse d'une saturation cognitive et ce, dans les domaines les plus enclins au déclin avec l'âge. Les données de la présente étude montrent cependant que l'hypothèse d'une adaptation stratégique avec l'âge responsable du maintien de la performance dans l'un des domaines cognitifs le plus préservé, notamment le langage expressif semble plus à même de rendre compte de l'ensemble de nos résultats (voir aussi Hills, Todd, & Goldstone, 2008, 2010 ; Mata & von Helversen, 2015). Cela revient donc à postuler que le compromis cognitif au cours du vieillissement est le résultat d'adaptations réussies entre les exigences du contexte cognitif et les ressources internes disponibles chez l'adulte âgé dans le but d'un maintien de l'efficience comportementale. D'ailleurs, l'expertise acquise de l'accumulation des connaissances sémantiques avec l'avancée en âge permet des adaptations cognitives augurant ainsi une sélection spontanée des stratégies *ad hoc*, et ce dans le but de maximiser le profit compte tenu des ressources disponibles (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010 ; Hedden et al., 2005 ; Reuter-lorenz & Cappell, 2008). Ce résultat est particulièrement important compte tenu du nombre restreint d'études ayant exploré les mécanismes de réorganisation neurofonctionnelle sous-jacents au maintien des habiletés langagières dans une tâche de fluence verbale. D'ailleurs, notre étude est la première à avoir explorer la signification fonctionnelle de la réorganisation cérébrale sous-jacents aux processus stratégiques contribuant à une tâche de fluence verbale (sémantique et orthographique) au cours du vieillissement. L'intégration de nos résultats dans les modèles neurocognitifs actuels du vieillissement montre que : 1) le phénomène HAROLD tel que révélé par Cabeza n'est pas limité aux régions frontales ; 2) la bilatéralisation de l'activité temporale contribuant au maintien de la performance sémantique de l'adulte âgé à un niveau comparable aux adultes jeunes ne reflète pas l'expression d'une surcharge cognitive qui viendrait soutenir la stratégie de regroupement mais vraisemblablement le reflet d'une adaptation stratégique basée sur un compromis cognitif entre la stratégie d'exploration (plus coûteuse) et celle d'exploitation plus avantageuse en termes de ressources disponibles et de la performance attendue par la tâche de fluence verbale.

Dans un autre ordre d'idées, on peut aussi souligner l'hypothèse de plasticité fonctionnelle de Greenwood (2007, 2010) qui permet d'expliquer le lien entre les mécanismes adaptatifs de la réorganisation neurofonctionnelle et cognitive au cours du vieillissement. Selon l'auteur, les réorganisations cérébrales résultent des changements de stratégies cognitives eux-mêmes corollaires des changements structuraux. Vraisemblablement, le mécanisme d'enchainements des adaptations cognitives et cérébrales proposé par Greenwood est à même de rendre compte du paradoxe selon lequel les régions frontales touchées précocement par le vieillissement peuvent aussi être sollicitées dans le maintien de la performance comportementale. Toutefois, cette hypothèse ne semble rien prédire à propos des domaines cognitifs les plus préservés (langage, mémoire sémantique, etc.) avec l'âge soutenus principalement par les régions cérébrales postérieures (cortex pariétal inférieur et cortex temporal moyen et inférieur postérieur) qui semblent conserver une meilleure intégrité anatomique et fonctionnelle dans le vieillissement (Raz et al., 1997). De plus, des études IRMf récentes ont révélé la contribution de ces régions cérébrales dans le traitement sémantique des mots et notamment dans les aspects exécutifs qui lui sont sous-jacents (Noonan, Jefferies, Visser, & Lambon Ralph, 2013 ; Binder, Desai, Graves, & Conant, 2009). Notre second travail correspondant aux études 2 et 3 a d'ailleurs pour objectif d'élargir l'exploration des mécanismes de réorganisation neurofonctionnelle sous-jacents aux aspects exécutifs du traitement sémantique des mots au cours du vieillissement en ayant recours à une tâche de catégorisation sémantique impliquant la capacité à maintenir un lien sémantique spécifique - qui varie selon le degré du contrôle requis - ou à le changer sur la base *de feedbacks* de l'expérimentateur.

6.3 Lien entre contrôle exécutif et sémantique dans le vieillissement : Deux trajectoires, une mission ?

Tel qu'abordé dans la première partie de la section théorique, la relation entre le contrôle cognitif et les connaissances sémantiques joue un rôle primordial dans la compréhension des changements qui opèrent au cours du vieillissement. Cependant, le lien neurofonctionnel qui se rapporte à l'interdépendance entre ces deux composantes cognitives demeure mal compris chez l'adulte âgé et notamment lorsque mise en jeu dans une tâche langagière de haut niveau. La mise en évidence des corrélats neuroanatomiques associés à la sémantique à travers la littérature en neuroimagerie fonctionnelle (Binder et al., 2009 ; Noonan et al., 2013) illustre l'interaction avec ceux du contrôle exécutif et suscite un regain d'intérêt dans le domaine du langage, notamment dans ses aspects lexico-sémantiques (Jefferies, 2013 ; Whitney et al., 2011 ; Roskies et al., 2001) et ceci dans un nombre très infime d'études sur le vieillissement sain. Dans une étude IRMf particulièrement intéressante portant sur la compréhension de phrases, Fedorenko, (2014) a étayé l'hypothèse de la réduction de l'espace d'interaction entre le langage et le contrôle cognitif. Au regard de cette hypothèse, les auteurs défendent l'idée selon laquelle les différences d'âge dans l'efficacité des processus de contrôle exécutif ne peuvent être révélées qu'en faisant appel à des tâches langagières de compréhension suffisamment exigeantes en termes de niveau de contrôle requis. Par conséquent, l'observation des déterminants de la réorganisation neurofonctionnelle sous-jacents aux aspects exécutifs du traitement sémantique des mots est à même de souligner les mécanismes responsables du maintien des habiletés lexico-sémantiques au cours du vieillissement. D'ailleurs, notre second travail correspondant aux études 2 et 3 a permis d'apporter quelques arguments convaincants quant à l'intérêt de l'utilisation d'une tâche langagière de haut niveau pour appréhender la signification fonctionnelle de la réorganisation neurofonctionnelle au cours du vieillissement.

Dans un contexte de changements neurofonctionnels et cognitifs au cours du vieillissement, le nombre restreint d'études IRMf sur le traitement sémantique montre qu'un maintien relatif de la performance dans une tâche de jugement (Stebbins et al., 2002) ou d'appariement sémantique (Peelle et al., 2013) est apparu davantage associé à des activations frontales plus bilatérales chez l'adulte âgé relativement aux adultes jeunes. De plus, Peelle et al., (2013) rapportent des activations accrues dans le cortex pariétal inférieur chez les adultes âgés performants comparativement à leurs homologues âgés moins performants ayant un pourcentage de précision de réponse plus faible en appariement sémantique. Ce patron d'activations fronto-pariétales reflète selon les auteurs la capacité des adultes âgés avec de meilleures performances sémantiques à solliciter les régions cérébrales dans le contrôle exécutif. Ces résultats concordent avec ceux de notre étude 2, lesquelles mettent en évidence un déplacement de l'activation cérébrale du cortex dorsolatéral préfrontal présente chez les jeunes vers le cortex pariétal inférieur chez les adultes âgés et ce, lors du changement vers un lien sémantique différent de celui précédemment maintenu.

Un nombre grandissant d'études en neuroimagerie fonctionnelle étaye l'hypothèse formulée sur le contrôle cognitif comme une fonction unitaire soutenu par un large réseau neuronal (*the unitary-function/neurally-distributed control hypothesis*). D'ailleurs, une distinction neurofonctionnelle a permis de souligner l'implication bilatérale du cortex préfrontal inférieur quand la tâche sémantique exige plus de contrôle (Wagner et al., 2001 ; Jefferies & Lambon Ralph, 2006). Par exemple, Badre et al. (2005) ont proposé l'existence de spécificités fonctionnelles du cortex préfrontal inférieur au sein duquel les portions ventrales (aire 47) sont impliquées dans la récupération contrôlée alors que les portions dorsale (aire 44/45) interviennent lorsque cela nécessite un accès à des représentation moins communes et ce, en surmontant la compétition avec d'autres représentations ayant une signification plus commune. Lors des tâches sémantiques impliquant la recherche des caractéristiques sémantiques spécifiques aux demandes de la tâche, Whitney et al., (2011) rapportent des activations du cortex temporal postérieur uniquement lorsqu'un contrôle est requis par le traitement sémantique. Toutefois, le cortex pariétal inférieur s'active lorsqu'un contrôle cognitif élevé est requis pour permettre un traitement cognitif efficient et ce, quelque soit la tâche (sémantique ou non-sémantique). En effet, l'implication du cortex pariétal inférieur a été soulignée à travers plusieurs domaines cognitifs (Noonan et al., 2013). Ces observations rejoignent, par ailleurs, le modèle de codage adaptatif proposé par Duncan (2001). L'idée principale de ce modèle repose sur la capacité adaptative d'un système neural responsable du traitement exécutif de traiter différents types d'informations et ce, à travers une large variété de domaines cognitifs. Autrement dit, une diversité de processus exécutifs conduit à des patterns d'activations similaires au sein des régions frontales (dorso et ventro-latérales) mais également dans les régions pariétales (gyrus angulaire et sillon intra-pariétal) ayant démontré la même capacité de codage adaptatif lorsqu'un niveau élevé de contrôle est requis. La mise en évidence dans notre second travail d'une différence d'âge dans l'implication des régions fronto-pariétales et notamment le cortex dorso et ventro-latéral ainsi que le cortex pariétal inférieur par les adultes âgés, notamment lorsque les processus exécutifs (maintien et de changement) qui sous-tendent le traitement sémantique des mots sont mis en œuvre illustre le caractère adaptatif du système du contrôle exécutif dans le maintien de la performance sémantique au cours du vieillissement. En fait, l'hétérogénéité des manifestations neurofonctionnelles associé à l'interdépendance autant neurofonctionnelle que cognitive entre le langage et le contrôle exécutif revêt une importance capitale dans les études sur le vieillissement.

6.4 Pertinence scientifique et clinique

Ce travail de recherche en neurosciences cognitives apporte un nombre appréciable d'observations dans le domaine du langage, notamment en ce qui concerne les mécanismes de réorganisation neurofonctionnelle sous-jacents au maintien des habiletés du traitement sémantique des mots au cours du vieillissement. Un ensemble d'aspects méthodologiques et théoriques distinguent le présent travail. Tout d'abord, l'approche neurofonctionnelle et comportementale basée sur une analyse des stratégies mises en jeu lors de la tâche de fluence verbale (sémantique et orthographique) n'a, jusqu'à présent, jamais été examinée dans un contexte de vieillissement. D'ailleurs, l'utilisation d'un design mixte (bloc/évènementiel) d'acquisition des données IRMf a permis pour la première fois de mieux cerner la signification fonctionnelle de la réorganisation cérébrale observée chez l'adulte âgé lors de la mise œuvre spontanée et auto-initiée des stratégies. Enfin, le choix d'un mode d'évocation expressif et auto-rythmé au lieu d'un mode d'évocation contrôlé par l'expérimentateur a permis une exploration et une exploitation optimales du savoir dans le but de se rapprocher davantage des conditions adoptées en situation clinique. Ce faisant, l'exploration des mécanismes de réorganisation neurofonctionnelle dans notre premier travail et ce, par le biais d'une tâche de production langagière de haut niveau a permis de mettre en évidence l'hétérogénéité des trajectoires de changements de l'activation cérébrale au cours du vieillissement.

De façon plus générale, en accord avec une récente littérature en neuroimagerie fonctionnelle (Noonan et al., 2013; Whitney et al., 2011; Wagner et al., 2001, Binder et al., 2009), les résultats de notre second travail indiquent l'importance de considérer l'interdépendance entre le contrôle exécutif et le traitement sémantique par le biais de tâches langagières de haut niveau et notamment celles qui requièrent des degrés variables de contrôle exécutif.

6.5 Limites et perspectives de recherche

Le présent travail de thèse comprend certaines limites mais dont la prise en considération pourrait permettre aux futures études en neurosciences cognitives du vieillissement d'élargir la compréhension des déterminants cognitifs et neurofonctionnels sous-jacents au maintien des habiletés de traitement sémantique des mots. Dans notre première étude sur la fluence verbale, une correspondance entre la réorganisation stratégique et les mécanismes de réorganisation neurofonctionnelle n'a pas pu être réalisé en fonction de la difficulté du critère de productivité (facile vs difficile) et ce, à cause d'une faible puissance statistique. Dans le même sens, en manipulant le degré de productivité, une étude comportementale portant sur la production orale des mots (Nikolai et al., 2017) a mis en évidence une différence dans la mise en jeu des processus stratégiques entre des catégories naturelles (animaux) et objets (vêtements) dans un groupe d'adultes âgés avec des plaintes cognitives subjectives. Les auteurs ont pu démontrer que l’analyse des processus stratégiques en fonction de la difficulté des catégories était un indicateur pertinent de la détection des déficits cognitifs plus subtils et ce, à des stades très précoces chez des adultes âgés ayant des plaintes subjectives. Enfin, les résultats obtenus dans notre second travail (études 2 et 3) ouvrent de larges perspectives de recherche. En effet, la contribution des ressources du contrôle exécutif dans le maintien des habiletés langagières nécessite des études supplémentaires pour élargir le développement des méthodes d’intervention pour traiter les déficits du traitement sémantique, notamment dans ses aspects exécutifs tel qu’observé en aphasie sémantique.

BIBLIOGRAPHIE

Abrams, L., & Farrell, M. T. (2011). Language processing in normal aging. The handbook of psycholinguistic and cognitive processes: Perspectives in communication disorders, 49-73.

Adrover-Roig, D., and Barceló, F. (2010). Individual differences in aging and cognitive control modulate the neural indexes of context updating and maintenance during task switching. *Cortex.* 46, 434–50. doi:10.1016/j.cortex.2009.09.012.

Adrover-Roig, D., Sesé, A., Barceló, F., and Palmer, A. (2012). A latent variable approach to executive control in healthy ageing. *Brain Cogn.* 78, 284–99. doi:10.1016/j.bandc.2012.01.005.

Angel, L., Fay, S., Bouazzaoui, B., and Isingrini, M. (2010). Individual differences in executive functioning modulate age effects on the ERP correlates of retrieval success. *Neuropsychologia* 48, 3540–3553. doi:10.1016/j.neuropsychologia.2010.08.003.

Antsey, K., Hofer, S., & Luszcz, M. (2003). Cross-sectional and longitudinal patterns of dedifferentiation in late-life cognitiveand sensory function: The effects of age, ability, attrition, and occasion of measurement. Journal of Experimental Psychology:General, 132, 470–487.

Badre, D., Poldrack, R. A., Paré-Blagoev, E. J., Insler, R. Z., and Wagner, A. D. (2005). Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. Neuron 47, 907–918. doi:10.1016/j.neuron.2005.07.023.

Banich, M. T., & Brown, W. S. (2000). A life-span perspective on interaction between the cerebral hemispheres. Developmental Neuropsychology, 18(1), 1-10.

Baltes, P. B. (1987). Theoretical propositions of life-span developmental psychology: On the dynamics between growth and decline. Developmental psychology, 23(5), 611.

Baltes, P. B., & Baltes, M. M. (1990). Psychological perspectives on successful aging: The model of selective optimization with compensation. In: P. B. Baltes & M. M. Baltes (Eds.), Successful aging: Perspectives from the behavioral sciences (pp. 1–34). New York: Cambridge University Press.

Baltes, P. B., & Lindenberger, U. (1997). Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging?. Psychology and aging, 12(1), 12.

Baudisch, A. (2009). How ageing is shaped by trade-offs (No. WP-2009-043). Max Planck Institute for Demographic Research, Rostock, Germany.

Berlingeri, M., Danelli, L., Bottini, G., Sberna, M., & Paulesu, E. (2013). Reassessing the HAROLD model: is the hemispheric asymmetry reduction in older adults a special case of compensatory-related utilisation of neural circuits? Experimental Brain Research, 224(3), 393-410. doi: 10.1007/s00221-012-3319-x

Bherer, L., Kramer, A. F., Peterson, M. S., Colcombe, S., Erickson, K., & Becic, E. (2005). Training effects on dual-task performance: are there age-related differences in plasticity of attentional control?. Psychology and aging, 20(4), 695.

Binder, J. R., Desai, R. H., Graves, W. W., and Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb. Cortex* 19, 2767–96. doi:10.1093/cercor/bhp055.

Bouazzaoui, B., Angel, L., Fay, S., Taconnat, L., Charlotte, F., and Isingrini, M. (2014). Does the greater involvement of executive control in memory with age act as a compensatory mechanism? *Can. J. Exp. Psychol.* 68, 59–66. doi:10.1037/cep0000005.

Braver, T. S., Barch, D. M., Keys, B. A., Carter, C. S., Cohen, J. D., Kaye, J. A., Janowsky, J. S., Taylor, S. F., Yesavage, J. A., Mumenthaler, M. S., et al. (2001). Context processing in older adults: evidence for a theory relating cognitive control to neurobiology in healthy aging. *J Exp Psychol Gen* 130, 746–763. doi:10.1037/0096-3445.130.4.746.

Braver, T. S., Braver, T. S., Reynolds, J. R., Reynolds, J. R., Donaldson, D. I., and Donaldson, D. I. (2003). Neural mechanisms of transient and sustained cognitive control during task switching. *Neuron* 39, 713–726. doi:10.1016/S0896-6273(03)00466-5.

Braver, T. S., and West, R. (2008). Working memory, executive control and aging. *Handb. Aging Cogn.*, 311–372.

Braver, T. S., Paxton, J. L., Locke, H. S., and Barch, D. M. (2009). Flexible neural mechanisms of cognitive control within human prefrontal cortex. *Proc. Natl. Acad. Sci. U. S. A.* 106, 7351–6. doi:10.1073/pnas.0808187106.

Bugg, J. M., Zook, N. A., DeLosh, E. L., Davalos, D. B., & Davis, H. P. (2006). Age differences in fluid intelligence: contributions of general slowing and frontal decline. Brain and cognition, 62(1), 9-16.

Burke, D. M., MacKay, D. G., Worthley, J. S., & Wade, E. (1991). On the tip of the tongue: What causes word finding failures in young and older adults?. Journal of memory and language, 30(5), 542-579.

Cabeza, R., Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., ... & Craik, F. I. (1997a). Age-related differences in neural activity during memory encoding and retrieval: a positron emission tomography study. Journal of neuroscience, 17(1), 391-400.

Cabeza, R. (2001b). Functional neuroimaging of cognitive aging. In R. Cabeza & A. Kingstone (Eds.), Handbook of functional neuroimaging of cognition (pp. 331-377). Cambridge: MIT Press.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage, 17(3), 1394-1402.

Cattell, R. B. (1963). Theory of fluid and crystallized intelligence: A critical experiment. Journal of educational psychology, 54(1), 1.

Chouiter, L., Holmberg, J., Manuel, A. L., Colombo, F., Clarke, S., Annoni, J.-M., & Spierer, L. (2016). Partly segregated cortico-subcortical pathways support phonologic and semantic verbal flu- ency: A lesion study. Neuroscience, 329, 275–283.

Collette, F., Hogge, M., Salmon, E., and Van der Linden, M. (2006). Exploration of the neural substrates of executive functioning by functional neuroimaging. *Neuroscience* 139, 209–21. doi:10.1016/j.neuroscience.2005.05.035.

Collette, F., and Salmon, E. (2014). Les modifications du fonctionnement exécutif dans le vieillissement normal. *Psychol. Fr.* 59, 41–58. doi:10.1016/j.psfr.2013.03.006.

Craik, F. I. M., & Lockhart, R. S. (1972). Levels of processing: A framework for memory research. Journal of verbal learning and verbal behavior, 11(6), 671-684.

Craik, F. I. M., & Byrd, M. (1982). Aging and cognitive deficits: The role of attentional resources. In F. I. M. Craik & S. Trehub (Eds.), Aging and cognitive processes (pp. 191–211). New York: Plenum.

Craik, F. I. M., & McDowd, J. M. (1987). Age differences in recall and recognition. Journal of Experimental Psychology. Learning, memory, and cognition, 13(3), 474-479.

Craik, F. I. M., and Bialystok, E. (2006). Cognition through the lifespan: Mechanisms of change. Trends Cogn. Sci. 10, 131–138. doi:10.1016/j.tics.2006.01.007.

Craik, F. I. M., & Bialystok, E. (2008). Lifespan cognitive development: The roles of representation and control. In F. I. M. Craik,& T. A. Salthouse (Eds.), The Handbook of Aging and Cognition (3rd ed., 2, pp. 557–601). Psychology Press.

Craik, F. I., & Rose, N. S. (2012). Memory encoding and aging: a neurocognitive perspective. Neuroscience & Biobehavioral Reviews, 36(7), 1729-1739.

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., and Cabeza, R. (2007). Que PASA? The posterior-anterior shift in aging. *Cereb. Cortex* 18, 1201–9. doi:10.1093/cercor/bhm155.

Davis, S. W., Kragel, J. E., Madden, D. J., & Cabeza, R. (2012). The architecture of crosshemispheric communication in the aging brain: linking behavior to functional and structural connectivity. Cerebral Cortex, 22(1), 232-242. doi: 10.1093/cercor/bhr123

Dennis, N. A., & Cabeza, R. (2008). Neuroimaging of healthy cognitive aging. In F. I. M. Craik & T. A. Salthouse (Eds.), Handbook of aging and cognition (pp. 1–54).

de Frias, C. M., Dixon, R. A., and Strauss, E. (2006). Structure of four executive functioning tests in healthy older adults. *Neuropsychology* 20, 206–214. doi:10.1037/0894-4105.20.2.206.

de Ribaupierre, A., & Ludwig, C. (2003). Age differences and divided attention: Is there a general deficit ? Experimental Aging Research, 29(1), 79-105.

Diaz, M. T, Rizio, A. A, & Zhuang, J. (2016). The neural language systems that support healthy aging: integrating function, structure, and behavior. Language And Linguistics Compass, 10(7), 314–334. doi:10.1111/lnc3.v10.7

Dolcos, F., Rice, H. J., & Cabeza, R. (2002). Hemispheric asymmetry and aging: Right hemisphere decline or asymmetry reduction. Neuroscience and Biobehavioral Reviews, 26(7), 819-825.

Duncan, J. (2001). An adaptive coding model of neural function in prefrontal cortex. Nature Reviews: Neuroscience, 2(11), 820-829.

Fedorenko, E. (2014). The role of domain-general cognitive control in language comprehension. Frontiers in psychology, 5, 335.

Geva, S., Jones, P. S., Crinion, J. T., Price, C. J., Baron, J. C., & Warburton, E. A. (2012). The effect of aging on the neural correlates of phonological word retrieval. Journal of cognitive neuroscience, 24(11), 2135-2146.

Goldstein, G., & Shelly, C. (2008). Does the right hemisphere age more rapidly than the left?, Journal of Clinical Neuropsychology, 3:1, 65-78, DOI: 10.1080/01688638108403114

Greenwood, P. M. (2000). The frontal aging hypothesis evaluated. Journal of the International Neuropsychological Society, 6(6), 705-726.

Greenwood, P. M. (2007). Functional plasticity in cognitive aging: Review and hypothesis. Neuropsychology, 21(6), 657–673.

Greenwood, P. M., & Parasuraman, R. (2010). Neuronal and cognitive plasticity: A neurocognitive framework for ameliorating cognitive aging. Frontiers in Aging Neuroscience, 2(NOV), 1–14.

Grady, C. L., Maisog, J. M., Horwitz, B., Ungerleider, L. G., Mentis, M. J., Salerno, J. A., et al. (1994). Age-related changes in cortical blood flow activation during visual processing of faces and location. Journal of Neuroscience, 14(3), 1450-1462.

Hedden, T., & Gabrieli, J. D. E. (2004). Insights into the ageing mind: A view from cognitive neuroscience. Nature Reviews. Neuroscience, 5(2), 87–96. doi:10.1038/nrn1323

Hedden, T., & Yoon, C. (2006). Individual differences in executive processing predict susceptibility to interference in verbalworking memory. Neuropsychology, 20(5), 511–528.

Herd, S. A., O'Reilly, R. C., Hazy, T. E., Chatham, C. H., Brant, A. M., and Friedman, N. P. (2014). A neural network model of individual differences in task switching abilities. *Neuropsychologia* 62, 375–389. doi:10.1016/j.neuropsychologia.2014.04.014.

Hills, T. T, Todd, P. M, & Goldstone, R. L. (2008). Search in external and internal spaces. Psychological Science, 19(8), 802–808. doi:10.1111/j.1467-9280.2008.02160.x

Hills, T. T., Todd, P. M., & Goldstone, R. L. (2010). The Central Executive as a Search Process: Priming Exploration and Exploitation Across Domains. Journal of Experimental Psychology: General, 139 (4), 590–609. doi:10.1037/a0020666

Hoffman, P., & Morcom, A. M. (2017). Age-related changes in the neural networks supporting semantic cognition: A meta-analysis of 47 functional neuroimaging studies. Neuroscience & Biobehavioral Reviews.

Hull, R., Martin, R. C., Beier, M. E., Lane, D., and Hamilton, A. C. (2008). Executive function in older adults: A structural equation modeling approach. *Neuropsychology* 224, 508–522. doi:10.1037/0894-4105.22.4.508.

Hurks, P. P. M., Schrans, D., Meijs, C., Wassenberg, R., Feron, F. J. M., & Jolles, J. (2010). Developmental changes in semantic verbal fluency: Analyses of word productivity as a function of time, clustering, and switching. Child Neuropsychology, 16(4), 366–387.

Hughes, D. L., & Bryan, J. (2002). Adult age differences in strategy use during verbal fluency performance. Journal of Clinical and Experimental Neuropsychology, 24(5), 642–654. doi:10.1076/ jcen.24.5.642.1002

Jefferies, E., and Lambon Ralph, M. A. (2006). Semantic impairment in stroke aphasia versus semantic dementia: a case-series comparison. *Brain* 129, 2132–47. doi:10.1093/brain/awl153.

Kennedy, K. M., Rodrigue, K. M., Bischof, G. N., Hebrank, A. C., Reuter-Lorenz, P. A., and Park, D. C. (2015). Age trajectories of functional activation under conditions of low and high processing demands: An adult lifespan fMRI study of the aging brain. *Neuroimage* 104, 21–34. doi:10.1016/j.neuroimage.2014.09.056.

Kopp, B., Lange, F., Howe, J., and Wessel, K. (2014). Age-related changes in neural recruitment for cognitive control. *Brain Cogn.* 85, 209–219. doi:10.1016/j.bandc.2013.12.008.

Krampe, R. T., & Ericsson, K. A. (1996). Maintaining excellence: deliberate practice and elite performance in young and older pianists. Journal of experimental psychology: general, 125(4), 331.

Lacombe, J., Jolicoeur, P., Grimault, S., Pineault, J., and Joubert, S. (2015). Neural changes associated with semantic processing in healthy aging despite intact behavioral performance. *Brain Lang.* 149, 118–127. doi:10.1016/j.bandl.2015.07.003.

Li, S.-C., Lindenberger, U., & Frensch, P. A. (2000). Unifying cognitive aging: From neuromodulation to representation to cognition. Neurocomputing: An International Journal, 32-33, 879-890.

Li, K. Z. H., & Lindenberger, U. (2002). Relations between aging sensory/sensorimotor and cognitive functions. Neuroscience and Biobehavioral Reviews, 26(7), 777-783.

Lövdén, M., Bäckman, L., Lindenberger, U., Schaefer, S., & Schmiedek, F. (2010). A theoretical framework for the study of adult cognitive plasticity. Psychological bulletin, 136(4), 659.

Lustig, C., Hasher, L., & Zacks, R. T. (2007). Inhibitory deficit theory: Recent developments in a "new view." In D. S. Gorfein, C. M. MacLeod, D. S. (Ed) Gorfein, & C. M. (Ed) MacLeod (Eds.), Inhibition in cognition. (pp. 145–162). Washington, DC, US: American Psychological Association.

Marsolais, Y., Methqal, I., & Joanette, Y. (2015). Marginal neurofunctional changes in high-perform- ing older adults in a verbal fluency task. Brain and Language, 140, 13–23.

Marsolais, Y., Perlbarg, V., Benali, H., & Joanette, Y. (2014). Age-related changes in functional network connectivity associated with high levels of verbal fluence performance. Cortex, 58, 123-138.

Mata, R, & von Helversen, B. (2015). Search and the aging mind: the promise and limits of the cognitive control hypothesis of age differences in search. Topics In Cognitive Science, 7(3), 416– 427. doi:10.1111/tops.2015.7.issue-3

Mayr, U., & Kliegl, R. (2000). Complex semantic processing in old age: Does it stay or does it go? Psychology and Aging, 15(1), 29–43.

Meinzer, M., Flaisch, T., Seeds, L., Harnish, S., Antonenko, D., Witte, V., … Crosson, B. (2012). Same modulation but different starting points: performance modulates age differences in inferior frontal cortex activity during word-retrieval. PLoS ONE, 7(3), e33631. doi:10.1371/journal.pone.0033631

Meinzer, M., Flaisch, T., Wilser, L., Eulitz, C., Rockstroh, B., Conway, T., … Crosson, B. (2009). Neural signatures of semantic and phonemic fluency in young and old adults. Journal of Cognitive Neuroscience, 21(10), 2007–2018. doi:10.1162/jocn.2009.21219

Meinzer, M., Seeds, L., Flaisch, T., Harnish, S., Cohen, M. L., McGregor, K., . . . Crosson, B. (2012). Impact of changed positive and negative task-related brain activity on word retrieval in aging. Neurobiology of Aging, 33(4), 656-669. doi: 10.1016/j.neurobiolaging.2010.06.020

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., and Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex “Frontal Lobe” tasks: a latent variable analysis. *Cogn. Psychol.* 41, 49–100. doi:10.1006/cogp.1999.0734.

Morcom, A. M., Good, C. D., Frackowiak, R. S. J., & Rugg, M. D. (2003). Age effects on the neural correlates of successful memory encoding. Brain, 126, 213-229.

Nagels, A., Kircher, T., Dietsche, B., Backes, H., Marquetand, J., & Krug, A. (2012). Neural processing of overt word generation in healthy individuals: The effect of age and word knowledge. NeuroImage, 61(4), 832–840.

Navon, D., & Gopher, D. (1979). On the economy of the human-processing system. Psychological review, 86(3), 214

Noonan, K. A., Jefferies, E., Visser, M., & Ralph, M. A. L. (2013). Going beyond inferior prefrontal involvement in semantic control : evidence for the additional contribution of dorsal angular gyrus and posterior middle temporal cortex. Journal of Cognitive Neuroscience, 25(11), 1824–1850.

Park, D. C., Smith, A. D., Lautenschlager, G., Earles, J. L., Frieske, D., Zwahr, M., & Gaines, C. L. (1996). Mediators of long-term memory performance across the life span. Psychology and Aging, 11(4), 621–637. doi:10.1037/0882-7974.11.4.621

Park, D. C., Lautenschlager, G., Hedden, T., Davidson, N. S., Smith, A. D., & Smith, P. K. (2002). Models of visuospatial and verbal memory across the adult life span. Psychology and Aging, 17 (2), 299–320.

Peelle, J. E., Troiani, V., Wingfield, A., & Grossman, M. (2010). Neural processing during older adults' comprehension of spoken sentences: age differences in resource allocation and connectivity. Cerebral Cortex, 20(4), 773-782. doi: 10.1093/cercor/bhp142

Persson, J., Sylvester, C.-Y. C., Nelson, J. K., Welsh, K. M., Jonides, J., & Reuter-Lorenz, P. A. (2004). Selection requirements during verb generation: differential recruitment in older and younger adults. NeuroImage, 23(4), 1382-1390. doi: 10.1016/j.neuroimage.2004.08.004

Peelle, J. E., Chandrasekaran, K., Powers, J., Smith, E. E., & Grossman, M. (2013). Age-related vulnerability in the neural systems supporting semantic processing. Frontiers in Aging Neuroscience, 5(SEP), 1–11.

Raz, N., Gunning, F. M., Head, D., Dupuis, J. H., McQuain, J., Briggs, S. D., et al. (1997). Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. Cerebral Cortex, 7(3), 268-282.

Raz, N. (2000). Aging of the brain and its impact on cognitive performance: Integration of structural and functional findings. In F. I. M. Craik & T. A. Salthouse (Eds.), The Handbook of aging and cognition (2nd ed., pp. 1-90). Mahwah, NJ, US: Lawrence Erlbaum Associates.

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). Neurocognitive Aging and the Compensation Hypothesis. Current directions in psychological science, 17(3), 177-182. doi: 10.1111/j.1467-8721.2008.00570.x

Rypma, B., & D'Esposito, M. (2000). Isolating the neural mechanisms of age-related changes in human working memory. Nature Neuroscience, 3(5), 509-515.

Salthouse, T. A. (1991b). Reduced processing resources. In T. A. Salthouse (Ed.), Theoretical perspectives on cognitive aging (pp. 301-349). Hillsdale: Lawrence Erlbaum.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. Psychological Review, 103(3), 403-428.

Salthouse, T. A., Pink, J. E., & Tucker-Drob, E. M. (2008). Contextual analysis of fluid intelligence. Intelligence, 36(5), 464-486.

Sauzéon, H., Raboutet, C., Rodrigues, J., Langevin, S., Schelstraete, M. A., Feyereisen, P., . . . N'Kaoua, B. (2011). Verbal knowledge as a compensation determinant of adult age differences in verbal fluency tasks over time. Journal of Adult Development, 18(3), 144–154. doi:10.1007/s10804-010- 9107-6

Schunn, C. D., & Reder, L. M. (2001). Another source of individual differences: Strategy adaptivity to changing rates of success. Journal of Experimental Psychology: General, 130, 59–76.

Sörös, P., Bose, A., Sokoloff, L. G., Graham, S. J., & Stuss, D. T. (2011). Age-related changes in the functional neuroanatomy of overt speech production. Neurobiology of Aging, 32(8), 1505-1513. doi: 10.1016/j.neurobiolaging.2009.08.015

Stebbins, G. T., Carrillo, M. C., Dorfman, J., Dirksen, C., Desmond, J. E., Turner, D. A., Bennett, D. A., Wilson, R. S., Glover, G., & Gabrieli, J. D. (2002). Aging effects on memory encoding in the frontal lobes. Psychology and aging, 17, 44-55.

Thornton, R., & Light, L. L. (2006). Language comprehension and production in normal aging. In Handbook of the Psychology of Aging (Sixth Edition) (pp. 261-287).

Troyer, A. K., Moscovitch, M., & Winocur, G. (1997). Clustering and switching as two components of verbal fluency: Evidence from younger and older healthy adults. Neuropsychology, 11(1), 138–146.

Turner, G. R., & Spreng, R. N. (2012). Executive functions and neurocognitive aging dissociable patterns of brain activity. Neurobiology of aging, 33(4), 826-e1.

Tyler, L. K., Shafto, M. A., Randall, B., Wright, P., Marslen-Wilson, W. D., & Stamatakis, E. A. (2010). Preserving syntactic processing across the adult life span: The modulation of the frontotemporal language system in the context of age-related atrophy. Cerebral Cortex, 20(2), 352–364.

Unsworth, N., Spillers, G. J., & Brewer, G. A. (2011). Variation in verbal fluency: A latent variable analysis of clustering, switching, and overall performance. The Quarterly Journal of Experimental Psychology, 64(3), 447–466.

Vaughan, L., & Giovanello, K. (2010). Executive function in daily life: Age-related influences of executive processes on instrumental activities of daily living. Psychology and aging, 25(2), 343.

Velanova, K., Lustig, C., Jacoby, L. L., and Buckner, R. L. (2007). Evidence for frontally mediated controlled processing differences in older adults. *Cereb. Cortex* 17, 1033–1046. doi:10.1093/cercor/bhl013.

Verhaeghen, P., Steitz, D. W., Sliwinski, M. J., & Cerella, J. (2003). Aging and dual-task performance: A meta-analysis. Psychology and Aging, 18(3), 443-460.

Wagner, A. D., Paré-Blagoev, E. J., Clark, J., & Poldrack, R. A. (2001). Recovering meaning. Neuron, 31(2), 329–338.

West, R. L. (2000). In defense of the frontal lobe hypothesis of cognitive aging. Journal of the International Neuropsychological Society, 6(6), 727-729

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M. A., and Jefferies, E. (2011). The neural organization of semantic control: TMS evidence for a distributed network in left inferior frontal and posterior middle temporal gyrus. *Cereb. Cortex* 21, 1066–75. doi:10.1093/cercor/bhq180.

Whitney, C., Kirk, M., O'Sullivan, J., Lambon Ralph, M. a, and Jefferies, E. (2012). Executive semantic processing is underpinned by a large-scale neural network: revealing the contribution of left prefrontal, posterior temporal, and parietal cortex to controlled retrieval and selection using TMS. *J. Cogn. Neurosci.* 24, 133–47. doi:10.1162/jocn_a_00123.

Wierenga, C. E., Benjamin, M., Gopinath, K., Perlstein, W. M., Leonard, C. M., Rothi, L. J. G., Conway, T., Cato, M. A., Briggs, R., and Crosson, B. (2008). Age-related changes in word retrieval: Role of bilateral frontal and subcortical networks. *Neurobiol. Aging* 29, 436–451. doi:10.1016/j.neurobiolaging.2006.10.024.