UNIVERSITÉ DU QUÉBEC À TROIS-RIVIÈRES

LE SYSTÈME OLFACTIF CENTRAL AU SEIN DES PERSONNES À RISQUE DE DÉVELOPPER LA MALADIE D'ALZHEIMER

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Sommaire

La maladie d'Alzheimer (MA) est un enjeu de santé publique majeur, avec près de la moitié des personnes âgées de 65 ans et plus qui seront touchées par un trouble neurocognitif majeur lié à la MA d'ici 2060 (Rajan et al., 2021). Alors que la maladie débute des décennies avant l'apparition des premiers troubles de mémoire au stade de trouble cognitif léger (TCL) (Bateman et al., 2012; Jansen et al., 2015; Jia et al., 2024; Reiman et al., 2012; Villemagne et al., 2013), il est crucial d'identifier les individus à risque le plus tôt possible afin de maximiser l'efficacité des traitements émergents qui ciblent l'accumulation de la pathologie. Parmi les signes précoces de la maladie, on pourrait retrouver le trouble de l'identification olfactive. Des déficits aux tâches d'identification des odeurs sont fréquemment observé aux stades de trouble neurocognitif majeur et de TCL (Rahayel et al., 2012; Roalf et al., 2017). Cependant, il n'est pas clair à quel moment ce déficit olfactif apparait dans le continuum clinique de la MA, notamment s'il est déjà présent au stade de déclin cognitif subjectif (DCS) (Jessen et al., 2014). Cette thèse a pour objectif général de caractériser l'état du système olfactif central chez les personnes âgées à risque de développer un trouble neurocognitif majeur lié à la MA, ainsi qu'à caractériser la relation entre les déficits olfactifs et mnésiques. Dans le cadre de l'étude 1, nous avons réalisé une revue systématique et méta-analyse démontrant une atrophie du bulbe olfactif et du cortex olfactif primaire au sein des groupes TCL et MA comparativement aux personnes âgées sans trouble cognitif. La revue de la littérature a également révélé des défis méthodologiques pour l'analyse de ces régions. Pour pallier ces défis méthodologiques, lors de l'étude 2, nous avons effectué des analyses avancées

d'imagerie structurelle pour mesurer les sous-régions olfactives des structures cérébrales impliquées dans le traitement olfactif. Les résultats montrent des réductions volumétriques spécifique à ces sous-régions chez les individus avec un TCL, notamment le cortex piriforme, l'amygdale, le cortex entorhinal et l'hippocampe gauche. De plus, le volume de l'hippocampe gauche olfactif était corrélé aux scores de mémoire épisodique. L'étude 3 visait à évaluer l'identification olfactive au stade de DCS. Une méta-analyse a révélé une tendance vers une performance olfactive réduite chez les personnes âgées avec DCS par rapport aux groupes sans trouble cognitif. À l'aide d'une méta-analyse (étude 4), nous avons trouvé des associations significatives de faible amplitude entre les scores olfactifs et les scores de mémoire déclarative chez les personnes âgées sans trouble cognitif. Finalement au sein de l'étude 5, nous avons comparé l'identification olfactive entre des individus avec DCS et TCL, tout en évaluant la capacité prédictive de ces scores sur les scores en mémoire épisodique. Les résultats montrent que l'ajout de scores olfactifs à des modèles prédictifs améliore significativement la prédiction des performances en mémoire épisodique, tout en ayant une précision modérée pour distinguer les groupes DCS et TCL, avec une spécificité plus élevée (79 %) pour identifier le DCS (ou écarter le TCL). Enfin, cette thèse met en lumière les dommages précoces et spécifiques au système olfactif central dans le continuum de la MA, suggérant que l'identification olfactive pourrait constituer un marqueur du fonctionnement du système de mémoire déclarative, particulièrement la mémoire épisodique.

Table des matières

Liste des tableaux

Liste des tableaux dans l'Article 1

Tableau

Liste des tableaux dans l'Article 2

Tableau

Liste des tableaux dans l'Article 3

Tableau

Liste des tableaux dans l'Article 4

Tableau

Liste des tableaux dans l'Article 5

Tableau

Liste des figures

Liste des figures dans la thèse

Figure

Liste des figures dans l'Article 1

Figure

Liste des figures dans l'Article 2

Figure

Liste des figures dans l'Article 3

Figure

Liste des figures dans l'Article 4

Figure

Liste des figures dans l'Article 5

Figure

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[1] Voir Appendice.

Introduction générale

La maladie d'Alzheimer (MA) est une maladie neurodégénérative caractérisée par un déclin lent et progressif de nombreuses fonctions cognitives telles que la mémoire, le langage, le fonctionnement exécutif et les capacités visuospatiales. La MA est la principale cause de trouble neurodégénératif, représentant 60-80 % de ceux-ci (Alzheimer's Association, 2023). Une personne sur 9 (10,8 %) est atteinte du trouble neurocognitif majeur lié à la MA chez les personnes âgées de 65 ans et plus, cette proportion augmente à 13,1 % chez les personnes âgées entre 75 et 84 ans et à 33,3 % chez les personnes âgées de 85 ans et plus (Rajan et al., 2021). Étant donné le vieillissement de la population au Canada, on estime que la prévalence de cas de trouble neurocognitif augmentera de 65 % entre 2020 et 2030 (Alzheimer's Society, 2024). Aux États-Unis, on estime qu'en 2060 environ la moitié (48 %) des personnes âgées de 65 ans et plus aura un trouble neurocognitif majeur lié à la MA (Rajan et al., 2021). L'augmentation rapide du nombre de cas, tant au Canada qu'à l'international, aura d'importantes répercussions sociales et économiques. Il est primordial de mieux comprendre la maladie afin de trouver des moyens de la dépister précocement et d'y développer des traitements curatifs.

Neuropathologie

Sur le plan neuropathologique, on peut définir la MA par la présence d'accumulation de protéine β-amyloïde, qui formeront éventuellement des amas appelés plaques β-amyloïdes à l'extérieur des neurones, ainsi que de l'accumulation

d'enchevêtrements de la protéine tau à l'intérieur des neurones. Ces changements neurologiques mènent éventuellement à la neurodégénérescence du cerveau et à la mort neuronale. Ces trois types de dommages, soit l'accumulation de plaques β-amyloïde (A), d'enchevêtrement de la protéine tau (T) et la neurodégénérescence (N) sont caractéristiques de la MA (Jack et al., 2018).

Typiquement, l'accumulation de plaques β-amyloïdes apparait d'abord au sein de régions néocorticales comme le cortex orbitrofrontal médial, le cortex cingulaire postérieur et le précuneus, puis dans des régions temporales et limbiques comme le cortex entorhinal, l'hippocampe, l'amygdale et dans le cortex insulaire. Les plaques s'accumuleront finalement aux airs néocorticales associatives et sensorimotrices, les noyaux sous-corticaux, puis finalement le tronc cérébral et le cervelet (Grothe et al., 2017; Hanseeuw et al., 2018; Mattsson et al., 2019; Thal et al., 2002). En ce qui concerne la pathologie tau, les enchevêtrements neurofibrillaires sont d'abord confinés à la région transentorhinale et à la région CA1 de l'hippocampe (stades I-II), puis aux régions limbiques telles que le subiculum de la formation hippocampique et l'amygdale (stades III-IV), et enfin au néocortex (stades V-VI) (Braak & Braak, 1991; Lowe et al., 2020; Therriault et al., 2022). Ces dommages sont prédicteurs de l'atrophie cérébrale mesurée via l'imagerie par résonance magnétique (IRM) (Du et al., 2004; Gordon et al., 2018; La Joie et al., 2020; LaPoint et al., 2017; Pennanen et al., 2004; Whitwell et al., 2007, 2008).

Diagnostic neuropathologique VS clinique

En contexte de recherche, plusieurs études à devis longitudinaux ont détecté ces changements pathologiques des décennies avant l'apparition des symptômes et du diagnostic clinique (Bateman et al., 2012; Jansen et al., 2015; Jia et al., 2024; Reiman et al., 2012; Villemagne et al., 2013). Grâce à l'arrivée de nouveaux moyens de détecter ces biomarqueurs de manière *in vivo* via l'imagerie par tomographie par émission de positrons (TEP), les marqueurs sanguins ou plasmatiques et l'analyse du liquide céphalorachidien par ponction lombaire, il n'est plus nécessaire d'attendre la confirmation post-mortem afin de confirmer le diagnostic de MA (Jack et al., 2024). La présence de biomarqueurs β-amyloïdes et Tau suffisent à émettre le diagnostic de maladie d'Alzheimer, les symptômes cognitifs et comportementaux de la maladie (p. ex., troubles de mémoire) n'étant pas suffisamment spécifiques afin caractériser de la maladie. Cependant, bien que l'arrivée de ces technologies et nouveaux moyens diagnostics en contexte de recherche, en contexte clinique le diagnostic reste à ce jour « clinique » et se base sur les comportements et examens cognitifs mesurés et basés sur les critères de l'Institut national sur le vieillissement et l'Association sur l'Alzheimer (NIA-AA) (McKhann et al., 2011) et du DSM-V (American Psychiatric Association, 2015). Le diagnostic clinique probable de la MA, en l'absence d'une confirmation de tests positifs de la présence de pathologie β-amyloïdes et Tau, requiert les critères suivants :

1) Remplir les critères de troubles neurocognitifs majeurs (*dementia*) :
    a. Preuves d'un déclin cognitif significatif par rapport à un niveau antérieur de fonctionnement dans un ou plusieurs domaines cognitifs, basées sur :

i. Une préoccupation exprimée par le sujet lui-même, par un informateur fiable ou par le clinicien concernant une détérioration significative du fonctionnement cognitif; et

ii. Une altération marquée des performances cognitives, idéalement documentée par des tests neuropsychologiques standardisés ou, à défaut, par une évaluation clinique quantitative.

b. Les déficits cognitifs entravent l'autonomie dans les activités quotidiennes (c'est-à-dire qu'une assistance nécessaire pour accomplir des activités instrumentales complexes de la vie quotidienne telle que le paiement des factures ou la gestion des médicaments par exemple).

c. Les déficits cognitifs ne se produisent pas exclusivement dans le contexte d'un état confusionnel (délirium).

d. Les altérations cognitives ne sont pas mieux expliquées par un autre trouble mental (p. ex., un trouble dépressif majeur, une schizophrénie).

2) En plus de présenter les caractéristiques suivantes :

a. Apparition lente et progressive des symptômes, en opposition à une apparition brusque et soudaine;

b. Preuves d'un déclin cognitif significatif par rapport à un niveau antérieur;

c. Les déficits cognitifs initiaux et les plus marqués sont évidents dans l'une des catégories suivantes :

i. Présentation amnésique : C'est la présentation syndromique la plus courante de la maladie d'Alzheimer. Les déficits doivent inclure une

altération dans l'apprentissage et le rappel de l'information récemment apprise. Présence d'un déficit dans au moins un autre domaine cognitif.

ii. Présentations non amnésiques :

- Présentation langagière : Les déficits les plus marqués concernent le langage. Présence d'un déficit dans au moins un autre domaine cognitif.
- Présentation visuospatiale : Les déficits les plus marqués concernent les capacités visuospatiales. Présence d'un déficit dans au moins un autre domaine cognitif.
- Présentation exécutive : Les déficits les plus marqués concernent le domaine exécutif. Présence d'un déficit dans au moins un autre domaine cognitif.

d. Le diagnostic probable de la maladie d'Alzheimer ne doit pas être posé en présence de signes ou preuves d'une autre étiologie (p. ex., démence à corps de Lewy, démence vasculaire, trouble neurodégénératif d'étiologie mixte, etc.).

Continuum clinique de la maladie d'Alzheimer

Tel que mentionné ci-haut, la MA progresse de manière lente et progressive. La pathologie se développe sur une période s'étalant sur des décennies avant l'apparition des premiers symptômes (Bateman et al., 2012; Jansen et al., 2015; Jia et al., 2024; Reiman et al., 2012; Villemagne et al., 2013). Avant d'atteindre le stade de trouble neurocognitif

majeur, l'individu progressera au sein de différents stades de la maladie. En 2018, le NIA-AA a proposé six stades cliniques de la MA qui s'inscrivent eux-mêmes au sein de trois stades syndromiques. Le premier stade syndromique caractérise les individus sans trouble cognitif (*cognitively unimpaired*), le deuxième stade correspond au stade de trouble cognitif léger (*mild cognitive impairment*) et le troisième stade est celui du trouble neurocognitif majeur (*dementia*) (Jack et al., 2018). Il est important de noter que ces trois catégories de syndromes sont utilisées afin de caractériser le statut cognitif et sont indépendantes de la présence ou absence de marqueurs pathologiques de la MA.

Stade 1 et 2 (sans trouble cognitif)

Les stades précliniques de la maladie d'Alzheimer se caractérisent en un niveau de performances cognitives qui demeurent statistiquement dans la normale lorsqu'ajustées en fonction de caractéristiques démographiques telles que l'âge, du sexe et le niveau d'éducation. Plus précisément, le stade 1 caractérise des individus asymptomatiques dont les performances cognitives sont dans la normale. Ces personnes ne rapportent aucun changement, ni inquiétude, au niveau de leur cognition. Dans le même ordre d'idée, leurs proches ne remarquent aucun changement chez la personne atteinte par la maladie.

Le stade 2 caractérise toujours des individus ayant des scores dans la normale au niveau des tests cognitifs objectifs. Cependant, ce stade est transitionnel vers le déclin cognitif et peut présenter des changements subtils dans certains domaines cognitifs comme la mémoire épisodique. Ces changements ne sont pas assez importants pour tirer

les performances cognitives d'un individu hors de la norme statistique. Bien que ce ne soit pas requis, sur le plan subjectif, les personnes se situant au stade 2 rapportent typiquement des inquiétudes et des changements d'une durée d'au moins six mois par rapport à leur niveau cognitif des dernières années. Ce changement peut aussi avoir été observé chez les proches du patient et être accompagné de changement de l'humeur, d'anxiété ou de motivation. Finalement, le stade 2 n'entraine aucun changement dans les activités de la vie quotidienne.

Le déclin cognitif subjectif

Le déclin cognitif subjectif (DCS) (*subjective cognitive decline,* ou *SCD* en anglais) est caractérisé par un déclin cognitif autorapporté en l'absence d'une atteinte cognitive objectivable aux différents tests cognitifs traditionnels (Jessen et al., 2014). Les critères de recherche afin de qualifier le DCS sont :

a. La présence d'une perception subjective d'un déclin cognitif par rapport au niveau de performance antérieur.
b. Dans le contexte d'un DCS au sein du continuum clinique de la MA, un niveau normal de performance cognitive est requis et doit être évalué à l'aide de tests cognitifs valides afin d'exclure la présence d'un trouble cognitif léger.

Afin de distinguer le DCS du vieillissement normal sans trouble cognitif, on ne se fie que sur la perception subjective de l'individu sur le déclin ou non déclin de ses capacités cognitives par rapport à un niveau antérieur.

Bien qu'étudié dans le contexte de la MA, le DCS n'est pas associé à une maladie spécifique. Lorsqu'on établit la présence de DCS, il est préférable d'ajouter dans lequel des contextes spécifiques celui-ci se réfère (p. ex., un DCS dans le prodrome de la MA). Ainsi, si l'on se base sur la description des différents stades du déclin cognitif au sein de la MA du NIA-AA (Jack et al., 2018), le DCS s'intègre au sein du stade 2 du continuum de la MA et peut représenter une sous-catégorie du stade de syndrome sans trouble cognitif.

Enfin, l'apparition d'un DCS n'est pas spécifique à un contexte de MA et ne garantit pas la progression vers un stade plus avancé de la maladie. En effet, il existe trois trajectoires possibles du DCS :

a. Le DCS se manifeste, mais il se rétablit complètement. Les fonctions cognitives objectives restent stables. Les conditions sous-jacentes du DCS peuvent être la conséquence d'enjeux affectifs, d'effets secondaires liés à une médication, être la conséquence de troubles du sommeil ou autres causes modifiables.
b. Le DCS se manifeste et se poursuit sans rémission et les fonctions cognitives objectives restent essentiellement stables. Le processus normal de vieillissement peut être une cause sous-jacente de ce type de DCS.
c. Le DCS se manifeste et les fonctions cognitives objectives se dégradent jusqu'à atteindre le niveau de trouble neurocognitif majeur. Cette détérioration peut être causée par une maladie neurodégénérative, y compris, la MA.

Stade 3 (Trouble cognitif léger)

Le stade 3 correspond aux individus ayant un trouble cognitif léger (TCL). Le TCL est caractérisé par des performances cognitives de niveau significativement plus faible que celui des personnes en santé cognitive du même groupe démographique. Le TCL peut également être attribué à un individu pour qui son niveau cognitif actuel se retrouve dans la normale, mais que ce niveau représente un déclin significatif par rapport à un niveau cognitif antérieur. Les individus au stade de TCL restent indépendants dans l'accomplissement de leurs activités au quotidien. Finalement, on estime que de 17 à 22 % des personnes âgées de 65 ans et plus ont un TCL (Manly et al., 2022; Petersen et al., 2018) dont la moitié serait positive aux marqueurs neuropathologiques de la MA (Petersen et al., 2013; Rabinovici et al., 2019). Cependant, tout comme le DCS, un diagnostic de TCL n'est pas garant ou spécifique d'une MA ni d'une progression éventuelle à un stade plus avancé de la maladie.

C'est la présence ou l'absence de trouble cognitif objectif qui distingue principalement les stades de DCS et de TCL. Il est suggéré d'utiliser non seulement le jugement clinique, mais également les résultats aux tests cognitifs afin d'assigner une personne à l'un des deux groupes (Jessen et al., 2020). Afin de distinguer les deux groupes sous la base des performances aux tests cognitifs, une coupure à -1,5 écart-type de la moyenne est utilisée si l'on mesure un domaine cognitif spécifique et -1 écart-type si l'on utilise plus d'un test pour le même domaine cognitif ou si l'on mesure au moins trois domaines cognitifs (Bondi et al., 2014).

Bien que ce ne soit plus nécessaire depuis la révision des critères de la MA par le NIA-AA (Jack et al., 2018), un déficit en mémoire épisodique est typiquement présent au sein du TCL dans un contexte de MA (Albert et al., 2011). Des performances en deçà de -1 ou -1.5 écart-type de la moyenne en rappel différé de l'information apprise auparavant sont typiquement retrouvées (Albert et al., 2011).

Stade 4, 5 et 6 (trouble neurocognitif majeur)

C'est à partir des stades 4, 5 et 6 que le déclin cognitif est substantiel et suffisamment sévère afin de nuire à l'autonomie quotidienne de la personne atteinte dans ces activités fonctionnelles. Le stade 4 est qualifié de léger et caractérise des atteintes progressives et substantielles sur différents domaines cognitifs et/ou comportementaux. Ainsi, cela engendre une perte d'autonomie pour certaines activités où l'aide d'un proche est nécessaire. Le stade 5 est qualifié de modéré et les atteintes cognitives ont un impact fonctionnel important sur la vie quotidienne. La personne atteinte n'est plus indépendante et nécessite une assistance fréquente dans les activités de la vie quotidienne. Finalement, le stade 6 est qualifié de sévère et est caractérisé par une dépendance complète en raison d'un impact fonctionnel grave sur la vie quotidienne, y compris les soins de base envers soi-même. C'est la perte d'autonomie dans les activités fonctionnelles du quotidien qui distingue le trouble neurocognitif majeur du trouble cognitif léger.

Atteintes cognitives liées à la maladie d'Alzheimer

Bien que les capacités attentionnelles, exécutives et visuospatiales peuvent être atteintes dans la MA, la présentation du syndrome de type amnésique est la plus courante (Reed et al., 2007), touchant différents processus de la mémoire déclarative.

La mémoire déclarative fait référence à la capacité de se souvenir consciemment et de façon explicite de faits, d'évènements ou de connaissances. Elle comprend à la fois la mémoire épisodique et la mémoire sémantique. Selon le modèle de Tulving, ces deux types de mémoire sont relativement indépendant. De son côté, la mémoire épisodique concerne les souvenirs d'informations provenant d'évènements personnellement vécus dans un contexte spatio-temporel particulier (p. ex., se souvenir d'avoir fermé le four de la cuisine après avoir cuisiné), tandis que la mémoire sémantique fait référence aux faits, concepts et connaissances générales indépendamment d'un contexte spatio-temporel (p. ex., savoir que les couleurs officielles du club de hockey des Canadiens de Montréal sont le bleu, le blanc et le rouge) (Tulving, 1972). D'un point de vue davantage basé sur la neurobiologie, le modèle de Squire et Zola-Morgan propose que les composantes épisodique et sémantique sont interreliées, du fait qu'ils reposent tous les deux sur un réseau cérébral commun centré sur du lobe temporal médian, incluant notamment l'hippocampe au moment de l'encodage (Squire & Zola-Morgan, 1991).

La mémoire épisodique peut se diviser en trois sous-composantes : l'encodage, la stockage (ou emmagasinage) et la récupération. L'encodage implique la conversion de

l'information perçue par nos sens en traces mnésiques susceptibles d'être conservées dans la mémoire à long terme. Après l'encodage initial, la consolidation de l'information permet son stockage à long terme. Finalement, la récupération est le processus par lequel les informations stockées en mémoire à long terme sont récupérés. Bien que l'ensemble de ces processus soient affectés dans la MA, c'est principalement les processus de d'encodage et de stockage de l'information qui sont touchés, pouvant apparaitre des années avant le diagnostic clinique de la MA (Albert et al., 2001; Bäckman et al., 2001; Grober et al., 2008). Les patients ont donc de la difficulté à créer de nouveaux souvenirs et à les stocker en mémoire à long terme, et ce, même en situation facilitant l'encodage (Buschke et al., 1997; Lekeu et al., 2003). Une méta-analyse a démontré que les tâches de rappel différé de listes de mots sont d'ailleurs les meilleurs prédicteurs neuropsychologiques d'une conversion du stade de trouble cognitif léger au stade de trouble neurocognitif majeur de type Alzheimer (Belleville et al., 2017).

Ces atteintes précoces de la mémoire épisodique peuvent être expliquées en partie par des dommages se produisant très tôt dans la maladie aux régions limbiques et temporales supportant la mémoire épisodique comme l'hippocampe, le gyrus parahippocampique et le cortex entorhinal (Gabrieli et al., 1997; Squire & Zola, 1991, 1996). En effet, chez des adultes âgés sans trouble cognitif, le niveau d'accumulation de pathologie tau, particulièrement au sein du lobe temporal médial, le gyrus parahippocampal et le cortex entorhinal est associé à la performance en mémoire épisodique (Maass et al., 2018). Au sein du devis longitudinal de la même étude, le degré et la progression de l'atrophie du

cortex entorhinal suivaient la progression de la pathologie tau et du déclin en mémoire épisodique (Maass et al., 2018). Des résultats similaires ont été retrouvés au sein d'autres études où le niveau de pathologie tau étaient associé à un déclin de la mémoire épisodique (Aschenbrenner et al., 2018; Marks et al., 2017; Tanner et al., 2022). La pathologie amyloïde jouerait davantage un rôle de médiateur, amplifiant l'association entre la pathologie tau et le déclin cognitif (Aschenbrenner et al., 2018; Marks et al., 2017). Finalement, il a été bien documenté au cours des dernières décennies que les atrophies de matière grise des régions du lobe temporal médial comme l'hippocampe et le cortex entorhinal sont liées à la performance en mémoire épisodique chez une population avec la maladie d'Alzheimer (Paola et al., 2007), un TCL (Epelbaum et al., 2018; Leube et al., 2008; Sexton et al., 2010), un DCS (Caillaud et al., 2019, 2023; Epelbaum et al., 2018) et chez les personnes âgées sans trouble cognitif (Rosen et al., 2003). Ces atrophies prédisent le déclin en mémoire à plus long terme (Chauveau et al., 2021; Planche et al., 2021).

La mémoire sémantique est également atteinte au sein de la MA, et ce, même au stade de TCL (Delage et al., 2020). Les déficits de mémoire sémantique dans la MA sont souvent évalués à l'aide de tâches de dénomination, de catégorisation et d'identification d'objets. Les patients peuvent montrer une difficulté accrue à se souvenir des noms des objets et des personnes, une confusion entre des concepts similaires ou une incapacité à comprendre des termes autrefois familiers. Ce déclin sémantique peut être expliqué par des dommages précoces au niveau de régions qui sous-tendent le réseau neuronal sémantique (Ralph et al., 2017). Par exemple chez des patients avec un TCL, de plus

faibles scores en mémoire sémantique ont été associés à une réduction du volume de matière grise au sein du cortex préfrontal inférieur et le lobe temporal antérieur gauche (Joubert et al., 2010), ainsi qu'à de l'hyperactivation au niveau de régions comme le lobe temporal antérieur, le gyrus fusiforme droit, le cortex préfrontal inférieur et la partie postérieure du gyrus temporal moyen (Pineault et al., 2018).

Traitement et enjeux liés à un diagnostic précoce de la maladie

En 2021, les résultats d'un essai clinique randomisé ont démontré qu'après 76 semaines, le Donanemab parvient à réduire considérablement l'accumulation de plaque β-amyloïde ainsi qu'à ralentir le déclin cognitif chez des individus en début de MA (Mintun et al., 2021). Des résultats similaires ont été observés avec le Lecanemab en 2023, traitement pouvant réduire de 27 % la progression de la maladie (van Dyck et al., 2023). Ces traitements ciblent et facilitent l'élimination des plaques β-amyloïde via des mécanismes immunitaires, ralentissant le processus neurodégénératif. Ainsi, il devient de plus en plus pertinent de détecter à l'avance les personnes à risque de développer un trouble neurocognitif majeur lié à la MA afin de pouvoir leur administrer les meilleurs traitements disponibles avant l'apparition des dommages cérébraux et des déficits cognitifs.

Bien que les mesures mêmes des biomarqueurs β-amyloïde et tau soient disponibles et prometteurs en contexte de recherche, il n'est pas possible, financièrement ou en termes d'infrastructure, d'utiliser des scanners cérébraux ou des ponctions lombaires en tant que

tests de dépistage sur toutes les personnes éligibles ou intéressées. Au cours des dernières années, de plus en plus de chercheurs se sont intéressés à des marqueurs simples d'usage, peu couteux et rapides afin de dépister les personnes à risque de développer un trouble neurocognitif majeur lié à la MA. La plainte subjective de difficultés cognitives, ou DCS, a été étudiée comme marqueur préclinique de la MA.

Le déclin cognitif subjectif comme marqueur précoce de la conversion au stade de trouble neurocognitif majeur

La plainte de mémoire subjective est considérée comme la première manifestation clinique de la MA (Jack et al., 2018; Jessen et al., 2014). Elle a été associée à plus de risque de déclin cognitif (Perna et al., 2023; Pike et al., 2021) et de présence de biomarqueurs positifs de la MA (Janssen et al., 2021; Pavisic et al., 2021; Wen et al., 2022). Ce stade est cependant hétérogène et ce n'est pas tous les individus rapportant un DCS qui ont les biomarqueurs positifs de la maladie, proportion qui peut varier entre 10 et 76 % (Ebenau et al., 2020; Jansen et al., 2021, 2022; Wolfsgruber et al., 2019). Sur le plan cognitif, ce n'est pas tous les individus avec un DCS qui « convertiront » vers un stade plus avancé de la maladie. En effet, bien que 10 % des personnes âgées de 45 ans et plus rapportent un DCS (Alzheimer's Association, 2023), et que ce nombre peut augmenter entre 50 et 80 % chez les adultes âgées de 70 ans et plus cognitivement normaux (Jessen et al., 2010; van Harten et al., 2018). Seulement 12 % des personnes âgées de moins de 75 ans avec un DCS convertissent vers le TCL ou le trouble neurocognitif majeur, 28 % chez ceux âgés de plus de 75 ans (Liew, 2020). Ainsi, bien qu'il représente un facteur de risque, la majorité des individus atteints de DCS ne

déclineront pas en trouble neurocognitif majeur. Pour mieux identifier les individus avec un DCS à risque de développer la MA, il a été proposé de combiner la plainte cognitive avec d'autres facteurs de risque de la maladie (Jessen et al., 2014, 2020). Une avenue potentielle serait de combiner le DCS avec le trouble de l'odorat associé à la MA.

Système olfactif

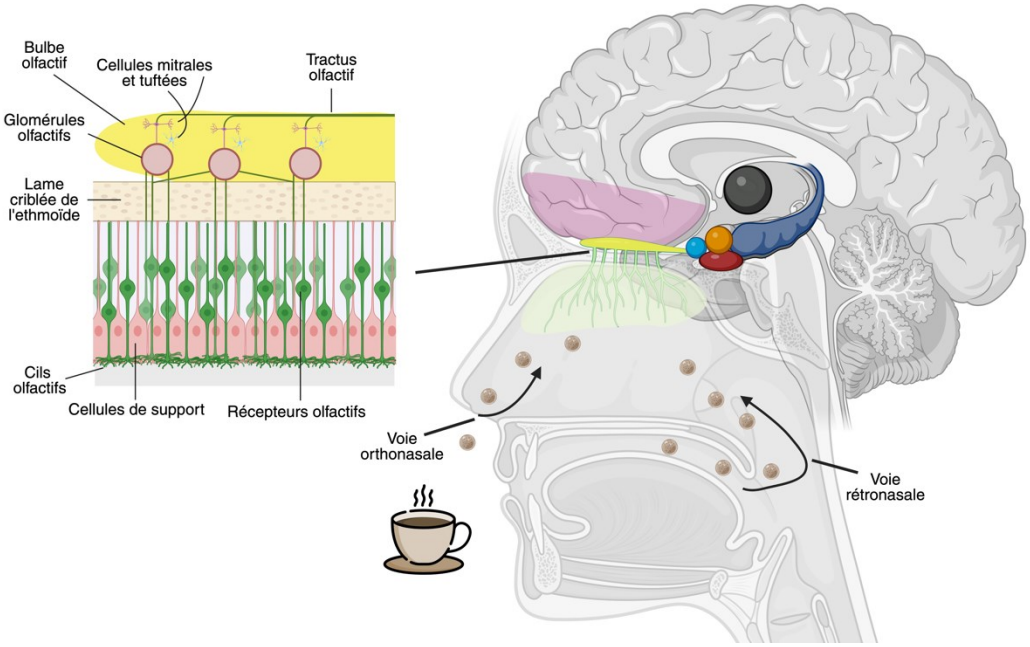
Le système olfactif nous permet de percevoir les odeurs de l'environnement. Il se compose de plusieurs structures et étapes de traitement, allant de la détection périphérique des molécules odorantes à leur traitement central au niveau du cerveau.

Système olfactif périphérique

La première étape afin de percevoir une odeur débute lorsque les molécules chimiques odorantes atteignent l'épithélium olfactif. L'épithélium olfactif est situé dans la partie supérieure de la cavité nasale et est une surface muqueuse composée notamment de neurones olfactifs. Les molécules odorantes peuvent atteindre l'épithélium olfactif par deux différentes voies : les voies orthonasale et rétronasale. Pour la voie orthonasale, les molécules passent via les narines et les cavités nasales afin de se diriger vers l'épithélium olfactif. Dans le cas de la voie rétronasale, les molécules s'acheminent à l'épithélium depuis la bouche via le nasopharynx, par exemple lorsque nous percevons les flaveurs de la nourriture que nous mangeons.

Figure 1.

Le système olfactif périphérique



Note. Le schéma illustre le système olfactif périphérique.

Une fois les molécules fixées sur les récepteurs des neurones olfactifs, l'information est transmise par les axones de ces neurones, qui forment le nerf olfactif (nerf crânien I). Ces axones franchissent la lame criblée de l'os ethmoïde pour atteindre le bulbe olfactif ipsilatéral, c'est-à-dire situé du même côté que la narine stimulée (Firestein, 2001). Au niveau du bulbe olfactif, l'information est relayée vers les cellules mitrales et tuftées, qui assurent un prétraitement de l'information olfactive (Cleland & Linster, 2005; Haberly, 2001). Contrairement à d'autres systèmes sensoriels comme la vision ou le toucher, qui projettent précocement de façon controlatérale (vers l'hémisphère cérébral opposé), les

projections olfactives initiales demeurent principalement ipsilatérales (vers l'hémisphère cérébral du même côté).

Système olfactif central

Une fois l'information olfactive transmise par les neurones sensoriels périphériques, elle est relayée au système olfactif central pour y être traitée. Ce système regroupe un ensemble de structures cérébrales impliquées dans l'analyse, l'intégration et l'interprétation des signaux olfactifs. Il comprend notamment le réseau olfactif primaire, qui inclut les cibles initiales des projections du bulbe olfactif, ainsi que plusieurs régions corticales et sous-corticales participant au traitement secondaire et à la modulation des informations olfactives.

Cortex olfactif primaire

Comme pour les autres modalités sensorielles, l'information olfactive parvient d'abord à un cortex primaire, c'est-à-dire une région corticale recevant directement les projections afférentes issues du système sensoriel concerné. Toutefois, le cortex olfactif primaire se distingue des autres cortex primaires (comme le cortex visuel primaire ou auditif primaire), notamment parce qu'il reçoit les projections directement du bulbe olfactif, sans relais préalable par le thalamus. De plus, ces régions primaires recevant des projections du bulbe olfactif incluent à la fois des structures corticales, comme le cortex piriforme, le cortex entorhinal et des portions du noyau olfactif antérieur, ainsi que l'amygdale qui est une structure sous-corticale sur le plan anatomique (Lundström et al.,

2011; Wilson et al., 2015). Ces régions ont également des connexions afférentes vers le bulbe olfactif, puis d'autres structures qui sont considérées comme faisant partie du réseau ou « cortex » olfactif secondaire. Ces structures incluent le cortex orbitofrontal, l'hippocampe, l'insula, le cortex périrhinal, le thalamus, l'hypothalamus, le striatum et le pallidum (Gottfried, 2010; Lundström et al., 2011).

Le cortex piriforme est la structure qui reçoit le plus de projections provenant du bulbe olfactif et a la particularité d'être une structure à trois niveaux appartenant au paléocortex (Vaughan & Jackson, 2014). Considéré comme une aire associative de l'information olfactive (Gottfried, 2010), le cortex piriforme serait responsable de la création « d'objets olfactifs » en synthétisant l'information des différents odorants ayant activé les neurones olfactifs (Wilson et al., 2015). Le cortex piriforme est également crucial dans le processus de séparation de l'objet olfactif de l'odeur ambiante (Wilson, 1998a, 1998b) et de l'effet d'habituation à court terme de cette dernière (Best et al., 2005; Yadon & Wilson, 2005). Ces processus seraient d'ailleurs possibles grâce à la capacité de plasticité synaptique du cortex piriforme (Gottfried, 2010; Wilson et al., 2015; Wilson & Stevenson, 2006). Le cortex piriforme et sa plasticité synaptique seraient également impliqués dans la mémoire associative olfactive (Barkai et al., 1994; Barkai & Hasselmo, 1997; Haberly, 2001; Saar et al., 2002). Il joue également un rôle dans l'évaluation subjective d'une odeur comme plaisante ou désagréable (Bensafi et al., 2007; Zelano et al., 2007).

L'amygdale est une structure sous-corticale du système limbique composée de différents sous-noyaux. Trois de ses sous-noyaux reçoivent des projections monosynaptiques directes du bulbe olfactif, c'est-à-dire le noyau médial, le noyau cortical et le complexe périamygdalien, justifiant leur inclusion dans le réseau ou « cortex » olfactif primaire. L'amygdale est principalement impliquée dans la valence hédonique et émotionnelle attribuée aux odeurs perçues, activée indépendamment de la valence hédonique attribuée (Gottfried et al., 2002; Lehman et al., 1980; Patin & Pause, 2015; Small et al., 1997; Torske et al., 2021).

Le cortex entorhinal reçoit des projections du bulbe olfactif et s'active lors de stimulation olfactive (Bensafi et al., 2008; Poellinger et al., 2001; Torske et al., 2021). Il projette à l'hippocampe et lui transmet le signal olfactif (Wilson et al., 2015). Les tâches en modalité olfactive requérant l'hippocampe sont altérées lors d'une lésion du cortex entorhinal (Staubli et al., 1984). Finalement, le cortex entorhinal jouerait également un rôle de modulation *top-down* vers le bulbe olfactif et le cortex piriforme (Insausti et al., 1997; Michael Wyss, 1981) et serait impliqué dans la navigation spatiale olfactive (Bao et al., 2019).

Tel que mentionné un peu plus haut, les régions du cortex olfactif primaire ont également des projections vers d'autres structures qui sont considérées comme le cortex olfactif secondaire. L'une des plus importantes est le cortex orbitofrontal. Le cortex orbitofrontal reçoit des projections directes du cortex piriforme (Ekstrand et al., 2001;

Illig, 2005; Johnson et al., 2000), mais également de manière indirecte via le thalamus (Krettek & Price, 1974; Price, 1985). Cette voie thalamo-orbitofrontale serait particulièrement impliquée dans l'attention olfactive (Plailly et al., 2008), des dommages à cette connexion altère la capacité à discriminer différentes odeurs (Courtiol & Wilson, 2015; Parnaudeau et al., 2018; Plailly et al., 2008). Le cortex orbitofrontal est principalement impliqué dans l'intégration multisensorielle (Gottfried & Zald, 2005; Kringelbach & Rolls, 2004) ainsi que dans des fonctions de hauts niveaux comme l'attribution d'une valeur ou signification motivationnelle envers certaines odeurs selon l'expérience et l'apprentissage via une modulation top-down vers le cortex piriforme (Critchley & Rolls, 1996; Rolls, 1999; Schoenbaum & Eichenbaum, 1995; Schoenbaum et al., 1999, 2011).

L'hippocampe, situé au sein du système limbique, est une autre structure clé du cortex olfactif secondaire notamment pour son implication pour la mémoire olfactive. L'hippocampe est particulièrement connecté structurellement et fonctionnellement au cortex olfactif primaire (Fjaeldstad et al., 2017; Zhou et al., 2021) et reçoit l'information olfactive via le cortex entorhinal (Schwerdtfeger et al., 1990; Staubli et al., 1984, 1986). Son implication a notamment été documentée au niveau de l'identification des odeurs (Aqrabawi et al., 2016; Aqrabawi & Kim, 2018; Kesner et al., 2011; Martin et al., 2007).

Trouble de l'odorat dans la maladie d'Alzheimer

Comme pour d'autres modalités sensorielles, un déclin olfactif est normalement observé au sein du vieillissement vers l'âge de 55 ans et plus (Oleszkiewicz et al., 2019). Alors que différents facteurs peuvent expliquer ce déclin, il peut notamment être expliqué par des processus neurodégénératives précoces, comme ceux de la MA. En effet, un symptôme moins connu de la MA est le trouble de l'odorat (Albers et al., 2015; Murphy, 2019). Pourtant, il a été estimé que le trouble olfactif serait présent chez environ 88 % des patients atteints de la MA (Woodward et al., 2017), chiffre pouvant même aller jusqu'à 100 % dans certaines études (Stamps et al., 2013).

Ce déficit olfactif s'exprime particulièrement lors des tâches d'identification des odeurs. En effet, bien que des réductions ont été observées au niveau de la capacité à détecter une odeur et de discriminer différentes odeurs, les réductions sont significativement plus importantes au sein des tâches d'identification et de reconnaissance des odeurs (Dhilla Albers et al., 2016; Rahayel et al., 2012). Les patients ont de la difficulté à identifier une odeur parmi un ensemble de quatre choix de réponses au sein des tests comme le *University of Pennsylvania Smell Identification Test* (UPSIT) (Doty et al., 1984), la batterie d'évaluation olfactive *Sniffin' Stick's Test* (Hummel et al., 1997) ou l'*AROMHA Brain Health Test* (Jobin et al., 2025). L'UPSIT (Doty et al., 1984) est un test nord-américain de type « *scratch & sniff* » composé de 40 vignettes odorantes microencapsulées, présentées sur des livrets. Il est largement utilisé pour sa sensibilité et sa robustesse normative. Le *Sniffin' Stick's Test* (Hummel et al., 1997), quant à lui, est

une batterie européenne qui évalue non seulement l'identification, mais aussi la détection et la discrimination olfactive à l'aide de stylos odorants. Enfin, *l'AROMHA Brain Health Test* (Jobin et al., 2025) est une batterie olfactive auto-administrable de manière digitale développée récemment, qui permet une évaluation rapide et accessible de l'odorat dans le cadre du dépistage précoce des troubles cognitifs.

Apparition précoce du trouble olfactif au sein de la MA

Le trouble de l'identification olfactive apparait de manière précoce au sein de la MA; deux méta-analyses ont démontré qu'il est déjà présent au stade de TCL (Jung et al., 2019; Roalf et al., 2017). Un score faible en identification olfactive au stade de TCL est également prédicteur de la progression au stade de trouble neurocognitif majeur (Albers et al., 2015). Des études ont démontré que la performance olfactive chez les personnes âgées sans trouble cognitif permettait même de prédire l'occurrence d'un TCL (Roberts et al., 2016; Wheeler & Murphy, 2021; Wilson et al., 2007).

Il n'est cependant pas tout à fait clair à quel stade de la MA ce déclin olfactif devient détectable. Quelques études ont mesuré la capacité d'identification olfactive chez des personnes âgées présentant le premier symptôme de la MA, le DCS. Certaines études ont démontré une réduction comparativement à un groupe contrôle de personnes âgées sans DCS (Chen et al., 2021; Sohrabi et al., 2009), alors que d'autres n'ont pas trouvé cette différence (Risacher et al., 2017; Tahmasebi, Zehetmayer, Pusswald et al., 2019; Tahmasebi, Zehetmayer, Stögmann et al., 2019).

Corrélats neuroanatomiques du trouble olfactif

Les troubles olfactifs observés dans les maladies neurodégénératives suivent souvent des altérations structurelles et fonctionnelles au sein des régions cérébrales clés. Des études neuropathologiques et en neuroimagerie ont permis de mieux caractériser les corrélats anatomiques spécifiques associés au déclin olfactif.

Bulbe olfactif

Le bulbe olfactif, le cortex entorhinal et les hippocampes sont parmi les premières structures touchées par la neuropathologie tau (Braak & Braak, 1991). Une étude histologique portant sur 138 personnes âgées sans troubles cognitifs, décédées, a examiné la relation entre la présence de neuropathologie amyloïde et tau dans le bulbe olfactif et les scores rétrospectifs d'identification olfactive (Tremblay et al., 2022). Les résultats ont montré une prévalence très élevée de la pathologie tau au niveau du bulbe olfactif (95 %, contre 27 % pour l'amyloïde). Toutefois, aucune relation significative n'a été observée entre la présence de cette pathologie et les scores olfactifs après avoir contrôlé l'effet de l'âge. Sur le plan de la neuroimagerie, peu d'études se sont concentrées sur la morphologie du bulbe olfactif au sein de la MA étant donné que la majorité des séquences d'IRM standards n'incluent pas des images complètes des bulbes olfactifs. Parmi celles-ci, certaines ont noté de plus faibles volumes du bulbe olfactif chez les patients au stade de trouble neurocognitif majeur comparativement aux personnes âgées sans trouble cognitif (Chen et al., 2018; Petekkaya et al., 2020; Thomann, Dos Santos, Seidl et al., 2009; Yu et al., 2015), alors qu'une autre n'a pas détecté cette différence (Servello et al., 2015). Le

même pattern s'observe au stade de TCL, certaines études ont trouvé une différence (Hang et al., 2014; Thomann, Dos Santos, Toro et al., 2009), alors que d'autres non (Servello et al., 2015).

Cortex entorhinal et hippocampe

La majorité des études explorant les corrélats neuroanatomiques du trouble olfactif précoce de la MA se sont intéressées au cortex entorhinal et à l'hippocampe. La morphologie de ces deux structures a été associé positivement à la performance d'identification olfactive au sein de participants dans le continuum clinique de la MA (Chen et al., 2021; Dhilla Albers et al., 2016; Murphy et al., 2003), particulièrement chez les participants avec un TCL (Dong et al., 2023; Papadatos & Phillips, 2023). Le score olfactif est associé à l'atrophie de ces régions (Tian et al., 2023).

Cependant, peu d'études ont testé ces associations spécifiquement à un stade précédent l'apparition des déficits mnésiques, comme le stade de DCS. Une étude a démontré une association entre l'épaisseur du cortex entorhinal et la performance en identification olfactive au sein d'un groupe de participants en DCS, association non présente avec le volume hippocampique (Papadatos & Phillips, 2023). Une autre étude également a démontré des associations entre de plus faibles volumes hippocampiques et épaisseur du cortex entorhinal ainsi que l'identification olfactive chez des personnes âgées sans trouble cognitif (Growdon et al., 2015).

Cortex piriforme

Étant donné la proximité anatomique du cortex piriforme avec les premières régions endommagées par la MA (p. ex., cortex entorhinal, hippocampes, amygdale) (Mai et al., 2015), et de l'important rôle du cortex piriforme au sein du traitement de l'information olfactive, on pourrait émettre l'hypothèse que cette structure est endommagée précocement au sein de la MA et que ces dommages pourraient expliquer en partie le trouble de l'identification olfactive retrouvé dans le trouble neurocognitif majeur et le TCL associé à la MA. Pourtant, très peu d'études se sont intéressées au cortex piriforme dans le décours de la MA, probablement parce que cette structure n'est pas incluse dans les atlas neuroanatomiques standards pour la neuroimagerie, par exemple les atlas inclus dans le populaire logiciel de neuroimagerie *Freesurfer* (p. ex., Desikan-Killiany, Destrieux, Harvard-Oxford, Automated Segmentation of Subcortical Structures, Brodmann Atlas).

Deux études ont directement examiné la morphologie du cortex piriforme chez des patients dans le continuum de la MA. Ces études ont mis en évidence une réduction des volumes de matière grise chez les patients atteints de trouble neurocognitif majeur associé à la MA (Al-Otaibi et al., 2021; Chen et al., 2021). Cette réduction a également été observée chez des patients présentant un TCL comparativement à des personnes âgées sans troubles cognitifs, mais était absente chez un groupe présentant un DCS (Chen et al., 2021). On retrouverait donc une atrophie du cortex piriforme au sein de la MA, il reste

cependant incertain si cette atrophie est détectable uniquement au stade de TCL ou également au stade de DCS.

Corrélats cognitifs du trouble olfactif

Bien qu'il ne soit pas clair si le trouble d'identification olfactive est détectable avant l'apparition des déficits de mémoire épisodique caractérisant le TCL, des études ont tenté d'examiner la relation entre le trouble d'identification olfactive et le déclin cognitif observé dans le vieillissement normal et pathologique. Les scores d'identification olfactive ont été associés aux scores de mémoire épisodique chez des patients au stade de TCL (Devanand et al., 2010; Papadatos & Phillips, 2023; Vyhnalek et al., 2015; Ward et al., 2017) et de trouble neurocognitif majeur (Makowska et al., 2011; Ward et al., 2017).

Peu d'études ont mesuré ces associations entre les scores d'identification olfactive et de mémoire épisodique au stade de DCS spécifiquement, l'une ayant retrouvé une relation significative (Papadatos & Phillips, 2023), alors qu'une autre n'a pas obtenu ce même résultat (Wang et al., 2021). Cependant, chez des personnes âgées sans trouble cognitif, le déclin et les fluctuations de performance de ces deux fonctions corrèlent à travers le temps (Dintica et al., 2021), particulièrement au sein des participants avec la présence de pathologie Alzheimer (Knight et al., 2020) et de l'allèle ApoE-4 (Olofsson et al., 2016, 2020).

Certains auteurs ont conceptualisé l'identification olfactive comme une fonction impliquant la mémoire sémantique des stimuli olfactifs, puisque l'identification olfactive repose sur les connaissances spécifiques préalables d'un individu pour identifier correctement l'odeur cible (Hedner et al., 2010; Larsson, 1997; Schab, 1991). Larsson et al. (2016) ont tenté de tester cette hypothèse. En testant différents modèles d'équations structurelles, ils ont conclu que l'identification olfactive serait mieux conceptualisée comme étant liée, mais distincte de la mémoire sémantique (Larsson et al., 2016). Cependant, dans le continuum clinique de la MA, il est moins clair si ces relations sont significatives. Une étude a retrouvé une association significative au stade de TCL (Papadatos & Phillips, 2023), alors qu'une autre ne l'a pas retrouvé (Wang et al., 2021). Au stade de DCS, aucune relation significative n'a été retrouvée (Papadatos & Phillips, 2023; Wang et al., 2021).

L'hypothèse des causes communes (*commun cause hypothesis*) pourrait expliquer un déclin commun de la mémoire déclarative et de l'identification olfactive au sein du vieillissement. Selon cette théorie, l'association entre la cognition et les capacités sensorielles augmenterait avec l'âge, étant donné les effets du vieillissement sur des structures cérébrales communes (Baltes & Lindenberger, 1997; Dulay & Murphy, 2002). En effet, la mémoire épisodique et l'identification olfactive sont toutes les deux supportées par des structures communes comme l'hippocampe et le cortex préfrontal, régions vulnérables au vieillissement et la MA (Bartsch & Wulff, 2015; Bettio et al., 2017; Braak & Braak, 1991; Thal et al., 2002). Prenant en compte cette théorie dans le contexte de la

MA, il est difficile de statuer si les relations entre le déclin cognitif et le déclin olfactif sont en dynamique de causalité l'un envers l'autre, ou bien si le déclin des deux capacités se produit davantage de manière parallèle due à des dommages à de structures clés communes. Il n'est également pas clair si ces associations sont présentes avant l'apparition des déficits mnésiques au stade de TCL.

Problématique

Alors que le trouble de l'identification olfactive est bien caractérisé au sein des patients atteints d'un TCL ou d'un trouble neurocognitif majeur associé à la MA, la littérature scientifique à ce jour ne peut statuer sur le début de ce déclin cognitif au sein du continuum clinique de la MA, notamment au stade de DCS. De plus, il n'est pas clair si des dommages au cortex piriforme, structure clé du traitement de l'information olfactive, sont présents chez les personnes au sein de ces groupes à risque de MA. Finalement, les déclins olfactifs et mnésiques sont deux symptômes précoces de la MA, mais il n'est pas clair si l'un débute avant l'autre et comment la mesure de l'identification olfactive peut être un indicateur du déclin cognitif.

Objectifs et hypothèses

Les objectifs principaux de cette thèse sont de (1) de caractériser l'état du système olfactif central chez les personnes âgées à risque de développer le trouble neurocognitif majeur lié à la MA; et (2) d'évaluer la relation entre le niveau de fonctionnement de la mémoire déclarative et du score en identification olfactive. L'hypothèse générale est celle

d'un déficit de l'identification des odeurs et de dommages structuraux des régions cérébrales associées (cortex olfactif primaire) chez les individus présentant un DCS ou un TCL. Le score olfactif sera associé à la mémoire déclarative, qui partage des réseaux neuronaux avec le système olfactif.

Les études 1, 2 et 3 visaient à répondre au premier objectif, soit la caractérisation du système olfactif central aux stades précoces de la MA. Les études 4 et 5 répondaient au second objectif, soit l'évaluation des liens entre les fonctions olfactives et la mémoire déclarative chez les personnes à risque de MA.

Article scientifique 1

Volumetry of Olfactory Structures in Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and a Meta-Analysis

Volumetry of Olfactory Structures in Mild Cognitive Impairment and Alzheimer's Disease: A Systematic Review and a Meta-Analysis[2]

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Abstract

Olfactory decline is an early symptom of Alzheimer's disease (AD) and is a predictor of conversion from mild cognitive impairment (MCI) to AD. Olfactory decline could reflect AD-related atrophy of structures related to the sense of smell. The aim of this study was to verify whether the presence of a clinical diagnosis of AD or MCI is associated with a volumetric decrease in the olfactory bulbs (OB) and the primary olfactory cortex (POC). We conducted two systematic reviews, one for each region and a meta-analysis. We collected articles from PsychNet, PubMed, Ebsco, and ProQuest databases. Results showed large and heterogeneous effects indicating smaller OB volumes in patients with AD ($k = 6$, $g = -1.21$, 95% CI [−2.19, −0.44]) and in patients with MCI compared to controls. There is also a trend for smaller POC in patients with AD or MCI compared to controls. Neuroanatomical structures involved in olfactory processing are smaller in AD and these volumetric reductions could be measured as early as the MCI stage.

Keywords: olfactory bulb; primary olfactory cortex; Alzheimer's disease; MCI; MRI; meta-analysis

Introduction

Alzheimer's disease (AD) is the main cause of dementia in older adults (Alzheimer's Association, 2019). According to a large meta-analysis that included 119 studies, the overall point prevalence of dementia due to AD among individuals 60 and older is 40.2 per 1000 persons in community settings (Fiest et al., 2016). AD is a neurodegenerative pathology characterized by the accumulation of amyloid-β plaques and tau neurofibrillary tangles in the brain that leads to dementia (Jack et al., 2018). The neuropathology of AD begins 20 years or more before first cognitive symptoms appear (Jansen et al., 2015). At the behavioral level, it has been proposed that the first manifestation of AD neuropathology is a complaint of a recent cognitive change known as Subjective Cognitive Decline (SCD) (Jessen et al., 2014) before the manifestation of cognitive deficits known as Mild Cognitive Impairment (MCI) (Petersen et al., 2014). Although these early clinical stages are useful to better predict who is at risk of developing dementia related to AD, it would be important to find earlier and more specific markers. For instance, only 14% of individuals with SCD and 34% of those with MCI are expected to convert to dementia at least (Mitchell et al., 2014; Hu et al., 2017). Neurobiological damage related to AD that appears during a silent phase preceding SCD and MCI stages (Jansen et al., 2015; Bateman et al., 2012; Jack et al., 2013) first occurs in the transentorhinal and limbic regions (Benzinger et al., 2013; Braak & Braak, 1991), which are involved in memory and olfactory processing (Ferry et al., 2006; Maass et al., 2018; Rémy et al., 2005; Wilson et al., 2015).

The neuropathology of AD is driven by two processes: an extracellular accumulation of amyloid-β proteins (amyloid plaques) and an intracellular accumulation of hyper-phosphorylated tau proteins (neurofibrillary tangles) (Jack et al., 2018; Jack et al., 2016). Thal et al. (2002) suggest five phases of amyloid-β accumulation: it appears (1) first in the neocortex, (2) then in the allocortex and more precisely the entorhinal region, CA1 region of the hippocampus, and in the insular cortex, (3) then in subcortical nuclei, before involving (4) the brainstem, and (5) the pons and the cerebellum. Concerning tau pathology, Braak and Braak (1991) suggest five stages of tau accumulation. First, neurofibrillary tangles are confined to the transentorhinal region and the CA1 region of the hippocampus (stages I–II), then the limbic regions such as the subiculum of the hippocampal formation and the amygdala (stages III–IV), and finally to the isocortex (stages V–VI).

Neurodegeneration can be quantified using magnetic resonance imaging (MRI), which allows in vivo volumetric measurement of neuroanatomic structures. MRI data show that brain atrophy follows Braak staging and appears first in the medial temporal lobe, in the entorhinal cortex, followed by the hippocampus (Du et al., 2004; Jack et al., 2013; Maass et al., 2018; Whitwell et al., 2007) before progressing to other limbic regions and finally reaching the isocortex (Pini et al., 2016). Structural measurements of the medial temporal lobe can help to predict the progression to dementia in MCI patients (Detoledo-Morrell et al., 2004; Pennanen et al., 2004; Tapiola et al., 2008) and asymptomatic individuals (Stoub et al., 2005; Apostolova et al., 2010; Dickerson et al.,

2011). Hippocampal atrophy has long been considered a key early marker of Alzheimer's disease (De Leon et al., 1993; Petersen et al., 2000; Petersen et al., 1999). However, hippocampal atrophy is not specific to AD and can be found in other diseases such as Lewy body dementia, vascular dementia, Parkinson's dementia, and semantic dementia (Barber et al., 2000; Burton et al., 2009; Laakso et al., 1996; van De Pol et al., 2011). As a result, a single measurement of hippocampal atrophy is not sufficient to be a specific early marker of AD. Alternatively, combining the measurement of hippocampal atrophy with other brain structures that are also altered early in the course of the disease may help to improve the specificity of early biomarkers of AD (Frisoni et al., 2010; Johnson et al., 2012).

Olfactory dysfunction is an early clinical marker of AD (Murphy, 2019). Olfactory deficits, such as impaired olfactory identification, were found in both AD and MCI (Rahayel et al., 2012; Roalf et al., 2017). The presence of an impairment in olfactory identification capacity better predicts the conversion from MCI to dementia (Conti et al., 2013; Devanand et al., 2008). Recently, it has been found that olfactory identification could be altered as early as in the SCD stage (Jobin et al., 2021). Olfactory identification deficit might be the consequence of damage to central olfactory structures such as olfactory bulbs (OB) and the primary olfactory cortex (POC). Central olfactory processing starts with the reception of odorant information from nasal olfactory receptors to OB. Then, the OB project to the POC (i.e., piriform cortex, anterior olfactory nucleus, olfactory tubercle, anteromedial part of the entorhinal cortex, periamygdaloid cortex, anterior

cortical nucleus, and nucleus of the lateral olfactory tract of the amygdala; Lundström et al., 2011). The POC, more specifically the piriform cortex, sends direct input to the lateral entorhinal cortex (Carmichael et al., 1994), which responds to odorant stimulation (Xu & Wilson, 2012) and transmits olfactory information to the hippocampus (Wilson et al., 2015; Staubli et al., 1984). It has been found that both OB and POC exhibit AD-related damage. OB is the first central relay in the olfactory processing pathway, and typically exhibits amyloid-β deposition and neurofibrillary tangles in patients with AD or MCI (Attems & Jellinger, 2006; Kovács et al., 1999; Tsuboi et al., 2003). Structures of the POC and especially the entorhinal cortex were found to be atrophied in AD and MCI (Pennanen et al., 2004; Vasavada et al., 2015). The atrophy of the POC predicts the conversion to AD (Detoledo-Morrell et al., 2004; Dickerson et al., 2001; Stoub et al., 2010) and could help with the diagnosis of MCI (Traschütz et al., 2020). The atrophy of olfactory processing brain regions, such as OB and POC, could explain olfactory deficits in the course of AD. Measurement of such structures has the potential to become an early specific biomarker of AD when combined with hippocampal atrophy.

No systematic review or meta-analysis has addressed the volumetric loss of structures related to the sense of smell in the course of AD. The results of a systematic review and a meta-analysis could provide a neurobiological underpinning of the olfactory impairment that is commonly found in AD. In addition, a better characterization of the disease-specific atrophies in AD dementia and MCI stages may lead to the development of new biomarkers for the early detection of AD, which will be combined with measurements of brain

structures that are altered early in the course of the disease. Thus, the aim of the study was to verify whether the presence of a clinical diagnosis of AD or MCI is associated with an atrophy of OB and/or POC compared to healthy elderly from the same age group. We hypothesized that a smaller volume of OB and/or POC could be detected in AD and MCI compared to healthy controls.

Materials and Methods

This study has been conducted following PRISMA guidelines (Page et al., 2021). The protocol of this study was not registered.

Eligibility Criteria of the Selected Studies

Eligible studies were required to meet the following criteria: (1) contain an MRI measurement of OB and/or POC volumes, (2) include a clinical group (AD dementia or MCI) and a control group of cognitive healthy participants, and (3) both title and abstract had to be written in English.

Patients from AD groups had to meet the criteria for a clinical diagnosis of AD, characterized by a significant and progressive decline in two or more cognitive domains typically lead to memory deficits, behavioral symptoms, impairment of activities of daily living, and dementia (Dubois et al., 2010; McKhann et al., 1984).

Patients from MCI groups had to meet the criteria for a clinical diagnosis of MCI, characterized by the presence of cognitive or memory complaints, objective cognitive impairment, and a preserved independence in functional abilities that exclude dementia (Petersen, 2004; Petersen et al., 1999). Participants from the control groups were cognitively normal individuals.

Outcome

In each eligible study, total volume of both OB and /or POC had to be calculated from MRI scans by a manual or automatic segmentation from T1- or T2-weighted sequences.

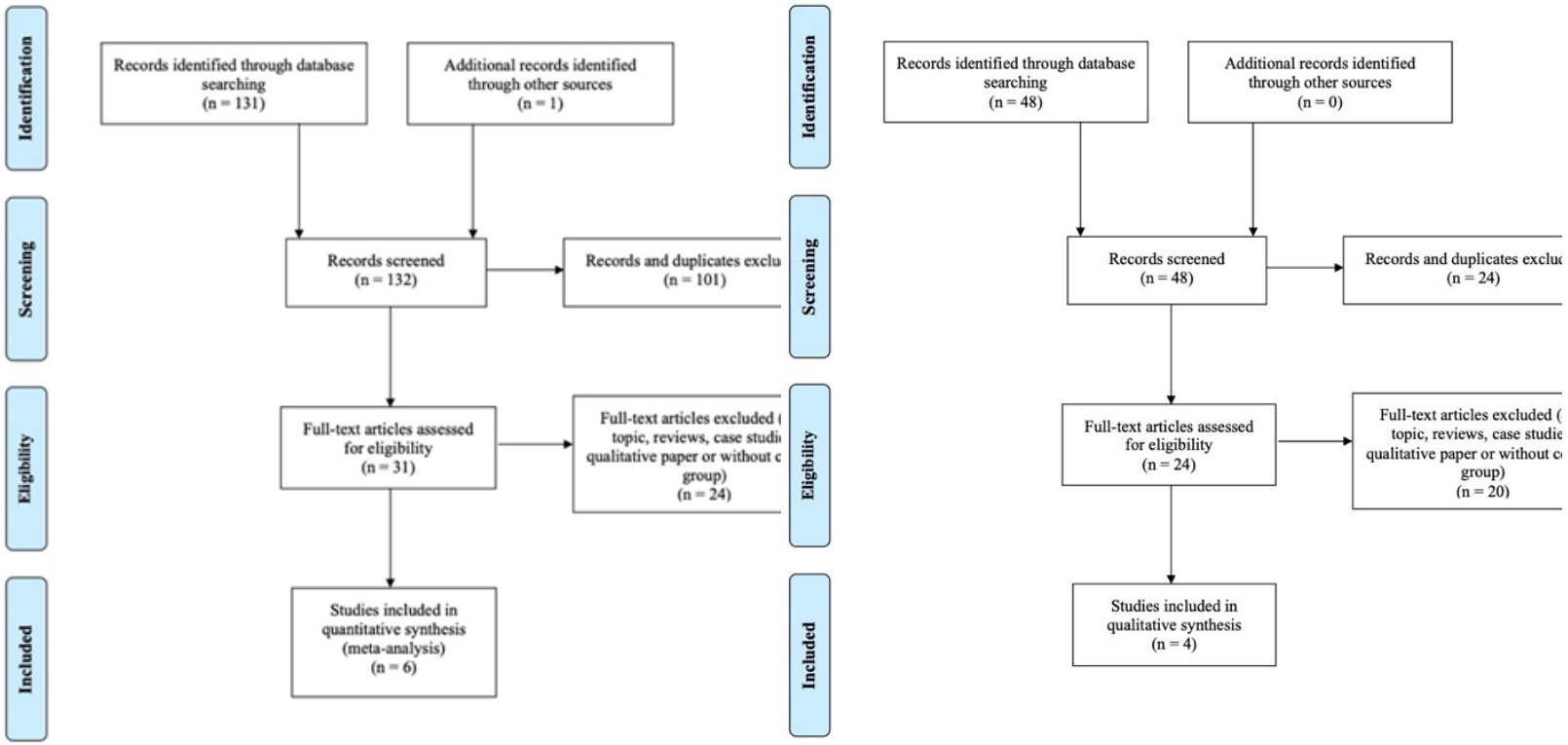
Search Strategy and Information Source

We searched for studies published up to February 2021 in PubMed, PsychNet, and Ebsco databases. Unpublished theses were found using the ProQuest Dissertations and Theses database. The following keywords were used: “Alzheimer”, “mild cognitive decline”, “MCI”, “MRI”, “volum*”, “thickness”, “olfactory bulb”, “olfactory cortex” using the following syntax: (“Alzheimer” OR “mild cognitive impairment” OR “MCI”) AND (“MRI” OR “volum*” OR “thickness”) AND (“olfactory bulb” OR “olfactory cortex”). We also used the snowballing method and examined reference lists from eligible studies found in databases. After excluding duplicated studies, we reviewed 93 studies for OB comparison and 39 studies for POC comparison (see Figure 1). We then excluded reviews, case studies, qualitative papers, and off-topic studies (e.g., animal studies, no

MRI data, absence of control group, etc.). As a result, 31 potentially eligible studies were identified for OB and 24 for POC.

Figure 1.

PRISMA Flowchart



(**a**) (**b**)

Note. (a) Flowchart illustrating the selection of OB studies. (b) Flowchart illustrating the selection of POC studies.

Study Selection and Risk of Bias in Individual Studies

Based on the eligibility criteria mentioned above, the first author (BJ) evaluated all of the selected studies. The first author then sent the list of potentially eligible studies to a research assistant who was blind to the purpose of the study. Articles were included if they were approved by both evaluators based on the risk of biased assessment.

The risk of bias of the selected studies was assessed using the Newcastle-Ottawa Scale (NOS; Peterson et al., 2011) as recommended (Zeng et al., 2015). The NOS is a tool to evaluate the quality of non-randomized case-control studies included in meta-analyses. Criteria were based on the evaluation of participants' selection, the comparability between groups, and the ascertainment of the quality of methods used to measure OB or POC volumes. It was agreed that the most conservative result would be selected when disagreements would emerge between both evaluators. No major disagreement emerged, and no studies were excluded following this evaluation. However, it has to be mentioned that both evaluators were unable to assess the risk of bias for two studies, as they were written in Chinese (Hang et al., 2014; Yu et al., 2015). These two studies were included in the eligible studies, as all relevant data for the meta-analysis were present in the abstracts written in English.

Analysis

We used Meta-Essentials (Suurmond et al., 2017) to perform analyses. We calculated Hedges' g to obtain a standardized effect size for each comparison using the mean

volumes and standard deviations reported in the eligible studies. When a study reported two volumes from the same structure (e.g., left and right volumes reported separately), a single effect size was calculated using the standard and recommended procedures (Borenstein et al., 2009) in order to avoid assigning more weight to studies with multiple outcomes. In this case, the effect size is computed as the mean of the left and right structure effect sizes:

$$\text{Mean effect size} = (\text{Hedges' } g1 + \text{Hedges' } g2) / 2$$

The variance of this mean is:

$$\text{Var (Mean effect size)} = \text{Var1} + \text{Var2} + 2r\sqrt{\text{Var1}}\sqrt{\text{Var2}}$$

In this equation, r is the correlation coefficient that describes the extent to which left and right structure volume covary.

Then, we calculated a combined effect size when the number of studies was appropriate (≥ 5; Borenstein et al., 2009). We followed recent guidelines for interpreting combined effect sizes as small ($g \geq 0.16$), medium ($g \geq 0.38$) and, large ($g \geq 0.76$) in geriatric populations (Brydges, 2019). We used the more conservative random effects model to compute the significance level of the mean effect sizes for each study.

Risk of Bias Across Studies

We qualified the presence of heterogeneity using Cochrane's Q-statistic and generated I^2 to quantify the degree of heterogeneity among effect sizes (Hedges & Olkin, 2014). We assumed heterogeneity if PQ was significant at $p < .05$. When heterogeneity was assumed and the number of included studies was sufficient (Fu et al., 2011), we then tested the effect of potential moderators such as age, sex, scanner type, software used to perform analyses, MRI sequences, and the type of view (sagittal vs. coronal) used.

We qualified publication bias using Rosenthal's failsafe-N test, which gives the number of potential unpublished studies required to render the combined effect size statistically insignificant or to change the conclusions of the meta-analysis (Rosenthal, 1979).

Results

Volumetry of the OB in Patients with AD

Study Selection and Characteristics

After analyzing full-text articles, six studies met the criteria for a total of 152 patients with AD and 166 controls (see Table 1).

Main Effect

After combining individual effect sizes, our analysis revealed a large effect size indicating smaller OB volumes in patients with AD compared to healthy older people ($k = 6$, $g = -1.21$, 95% CI [−2.19, −0.24]) that was significantly heterogeneous

($Q = 41.37$, $p_Q < 0.00$) (see Figure 2). Heterogeneity was confirmed by a second quantitative indicator ($I2 = 87.92\%$).

The Rosenthal's failsafe-N was 180 which is large and suggests no publication bias.

3.2. Volumetry of the OB in Patients with Mild Cognitive Impairment

3.2.1. Study Selection and Characteristics

For the comparison between patients with MCI and controls, we found three different studies for a total of 104 patients with MCI and 108 controls (see Table 2).

Table 1.

Characteristics of Studies Including Patients with AD in the Meta-Analysis on OB

Authors	Participants' Selection	Group Comparability	OB Measurement	Sample Size	Mean Age (SD)	OB Volume (SD)
Yu et al., 2015	N/A.	N/A.	N/A.	AD: 50 Controls: 50	N/A.	AD: 30.05 (5.08) Controls: 36.46 (4.11)
Chen et al., 2018	+ NINCDS-ADRDA criteria used by two trained neurologists. + Controls were from the same community. + Consecutive recruitment. − No description of controls' health history. −No measurement of AD-pathology biomarker (PET/CSF tau and amyloid-β)	+ Control for age, sex, education, and total intracranial volume.	+ Philips 3.0T MR scanner. + Sagittal 3D gradient-echo T1-weighted sequence. − Planimetric manual contouring. + Same method for both groups.	AD: 20 Controls: 25	AD: N/A. Controls: 55+	AD: 27.39 (3.22) Controls: 37.35 (4.04)
Petekkaya et al., 2020	+ NINCDS-ADRDA criteria. + Random recruitment of controls with equivalent for age and education level. + Controls without history of brain pathology or disease equivalent to AD or brain trauma, brain tumor, attacks, or clinical history with other accompanying psychological symptoms. −No measurement of AD-pathology biomarker (PET/CSF tau and amyloid-β).	+ Control for age and education level.	+ Philips 1.5T MR scanner. + 3D axial T1-weighted sequence. + Automatic parcellation of OB volumes using the IBASPM toolbox. + Same method for both groups.	AD: 9 Controls: 12	AD: 73.13 (4.73) Controls: 72.47 (3.35)	Left OB: AD: 0.84 (0.18) Controls: 1.04 (0.14) Right OB: AD: 0.85 (0.32) Controls: 1.21 (0.10)

Table 1.

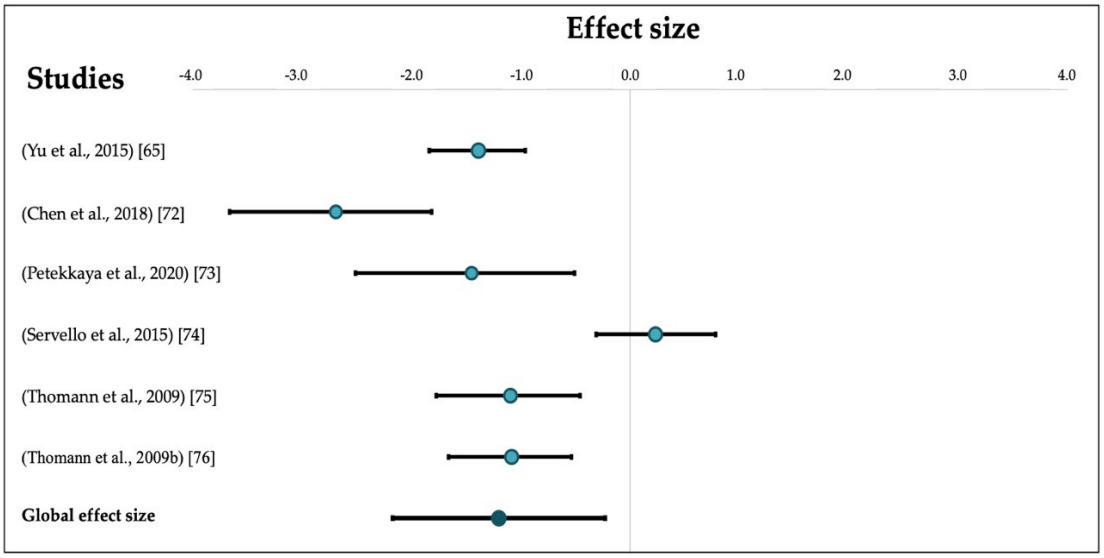
Characteristics of Studies Including Patients with AD in the Meta-Analysis on OB (continued)

Authors	Participants' Selection	Group Comparability	OB Measurement	Sample Size	Mean Age (SD)	OB Volume (SD)
Servello et al., 2015	+ NINCDS-ADRDA criteria. + Neuropsychological, radiological, and olfactory evaluation. + Controls were from the same community. + Recruitment between January and October 2013. − No random recruitment. − No description of controls' health history. −No measurement of AD-pathology biomarker (PET/CSF tau and amyloid-β).	− No control for sex, age, or other factors.	+ Siemens 3.0T MR scanner. +T1-weighted TSE coronal plane, T2-weighted TSE coronal plane, and T2 space 3d axial plane sequences + Manual segmentation of T1 and T2-weighted coronal sections. + Same method for both groups.	AD: 25 Controls: 28	AD: 73.7 (6.8) Controls: 69.4 (9.2)	AD: 35.91 (8.90) Controls: 33.49 (11.60)
Thomann et al., 2009	+ Ascertainment of personal/family history, physical, neurological, and neuropsychological examination. + NINCDS-ADRDA criteria. + Controls from the same community. + Recruitment between 2003 and 2004. − No consecutive/random recruitment. −No measurement of AD-pathology biomarker (PET/CSF tau and amyloid-β).	+ Control for age, gender, education, and total intracranial volume.	+ Siemens 1.5-T MR scanner. + T1-weighted 3D MPRAGE sequence. + Manual segmentation. + Same method for both groups.	AD: 21 Controls: 21	AD: 71.76 (4.94) Controls: 70.38 (7.14)	AD: 83.36 (9.01) Controls: 94.52 (11.26)
Thomann et al., 2009b	+ Ascertainment of personal/family history, physical, neurological, and neuropsychological examination. + NINCDS-ADRDA criteria for AD. + Controls from the same community and without cognitive complaints. + All participants were recruited between 2003 and 2004. + Controls were from the same community and without cognitive deficits. − No random recruitment. − No measurement of AD-pathology biomarker. (PET/CSF tau and amyloid-β).	+ Control for age, gender, education, and total intracranial volume.	+ Siemens 1.5-T MR scanner. + T1-weighted 3D MPRAGE sequence. + Manual segmentation. + Same method for both groups.	AD: 27 Controls: 30	AD: 71.44 (3.94) Controls: 70.50 (5.48)	AD: 85,92 (8.18) Controls: 95,73 (9,77)

Note. AD: Alzheimer's Disease, OB: Olfactory bulb, SD: Standard deviation, N/A.: Not available. NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

Figure 2.

Forest Plot of Effects Sizes for OB Volumetric Comparisons Between Patients with AD and Controls



Note. Error bars represent 95% Cis.

Table 2.

Characteristics of Studies Including Patients with MCI in the Meta-Analysis on OB

Authors	Participants' Selection	Group Comparability	OB Measurement	Sample Size	Mean Age (SD)	OB Volume (SD)
Hang et al., 2014	N/A.	N/A.	N/A.	MCI: 50 Controls: 50	N/A.	MCI: 36.47 (4.12) Controls: 46.71 (6.25)
Servello et al., 2015	+ Petersen criteria. + Neuropsychological, radiological, and olfactory evaluation. + Controls from the same community. + Recruitment between January and October 2013. − No random recruitment. − No description of controls' health history. − No distinction between amnesic and non-amnesic MCI. −No measurement of AD-pathology biomarker (PET/CSF tau and amyloid-β).	− No control for sex, age, or other factors.	+ Siemens 3.0T MRI scanner. +T1-weighted TSE coronal plane, T2-weighted TSE coronal plane, and T2 space 3d axial plane sequences. + Manual segmentation of T1 and T2-weighted coronal sections. + Same method for both groups.	MCI: 25 Controls: 28	MCI: 74.5 (7.5) Controls: 69.4 (9.2)	MCI: 34.87 (6.60) Controls: 33.49 (11.60)
Thomann et al., 2009b	+ Ascertainment of personal and family history, physical, neurological, and neuropsychological examination. + Controls from the same community. + Recruitment between 2003 and 2004. −No measurement of AD-pathology biomarker (PET/CSF tau and amyloid-β). − The aging associated cognitive decline was considered as a conceptual equivalent for MCI. Criteria were: (1) Performance of at least one standard deviation below the age-adjusted norm on a standardized test of cognition, (2) Exclusion of any medical, neurological, or psychiatric disorder that could lead to cognitive deterioration, (3) Normal activities of daily living, (4) No dementia. − No random recruitment. − No distinction between amnesic and non-amnesic MCI.	+ Control for age, gender, education, and total intracranial volume.	+ Siemens 1.5-T MR scanner. + T1-weighted 3D MPRAGE sequence. + Manual segmentation. + Same method for both groups.	MCI: 29 Controls: 30	MCI: 71.38 (6.14) Controls: 70.50 (5.48)	MCI: 90.81 (9.27) Controls: 95.73 (9.77)

Note. MCI: Mild Cognitive Impairment, OB: Olfactory bulb, SD: Standard deviation, N/A.: Not available.

Effect Sizes

We did not combine different effect sizes due to the small number of studies. In two studies (Zeng et al., 2015; Thomann et al., 2009), participants from the MCI group exhibited smaller OB volumes compared to controls ($g = -0.52$, 95% CI [−1.05, 0.00]; $g = -1.95$, 95% CI [− 2.45, −1.49]). However, in the third study (Servello et al., 2015), MCI patients exhibited larger OB volumes than controls ($g = 0.14$, 95% CI [−0.40, 0.69]).

All studies comparing OB volume between patients and controls used well-known clinical criteria to select their participants and the majority used a manual segmentation technique to measure OB volume. One study used an automatic parcellation of OB volumes (Petekkaya et al., 2020). Most studies measured OB volume controlling for factors such as total intracranial volume, age, sex, and education, except for one study that did not control for these factors (Servello et al., 2015).

Volumetry of the Primary Olfactory Cortex

Four studies met the criteria, but two studies used the same sample, leading to a total of three eligible samples. This prevented us from carrying out a formal meta-analysis. Again, all studies comparing POC volume between patients and controls used well-known clinical criteria or a clinical rating scale, to selected their participants. One study used an automatic to segmented the POC volume and two studies used a manual segmentation method. Each study measured OB volume controlling for factors such as total intracranial volume, age, sex, or education.

A general trend for smaller structures in both AD and MCI groups compared to the control groups is observed (see Table 3).

Table 3.

Characteristics of Studies Included in the POC Systematic Review

Authors	Participants' Selection	Group Comparability	POC Measurement	Sample Size	Mean Age (SD)	Outcome
Al-Otaibi et al., 2020	+ Diagnostic according to the National Institute on Aging—Alzheimer's Association (NIA-AA) criteria. + MMSE to qualify controls as cognitively normal. + Participants underwent a pre-screening visit including medical history questionnaire and blood analysis. − No random recruitment. − Poor description of control's recruitment. − No description of controls' health history. −No measurement of AD-pathology biomarker (PET/CSF tau and amyloid-β).	+ Control for sex, age, and education.	+ Siemens 1.5 T MR scanner. + T1-weighted sequence. + Automatic segmentation using the Automatic Anatomical Labelling atlas. Targeted structures: the olfactory tract, amygdala, piriform cortex, anterior perforated substance, the subcallosal area (including the subcallosal cingulate gyrus), and the anterior cingulate cortex. − Olfactory tract is included in the definition of the olfactory cortex although it is constituted of white matter. + Same method for both groups.	AD: 14 Controls: 25	AD: 75.06 (4.60) Controls: 71.1 (5.22)	Olfactory cortex volume is significantly smaller in patients with AD compared to healthy older controls. The decrease was more apparent in the left olfactory cortex.
Lu et al., 2019*	+ Use of the Clinical Dementia Rating, the MMSE, the CVLT-II, the Dementia Rating Scale and a reviewed of the medical records of AD and MCI patients. + Controls were from the same community and without cognitive deficits. − No random recruitment. − Poor description of control's recruitment. − No description of controls' health history. − No distinction between amnesic and non-amnesic MCI. −No measurement of AD-pathology biomarker (PET/CSF tau and amyloid-β).	+ Control for age.	+ Siemens Trio 3.0 T scanner. + T1-weighted MPRAGE sequence. − Manual segmentation. Targeted structures: the anterior olfactory nucleus, olfactory tubercle, piriform cortex, anterior portion of the periamygdaloid cortex, amygdala, and anterior perforated substance. + Same method for both groups.	AD: 26 EMCI: 36 LMCI: 31 Controls: 44	AD: 71.55 (7.3) EMCI: 71.69 (7.3) LMCI: 72.41 (7.4) Controls: 74.18 (6.1)	There was a decreasing trend for a smaller POC volume dependent on AD disease state, but no difference reach significance (Controls > LMCI > EMCI > AD).

Table 3.

Characteristics of Studies Included in the POC Systematic Review (continued)

Authors	Participants' Selection	Group Comparability	POC Measurement	Sample Size	Mean Age (SD)	Outcome
Vasavada et al., 2015	+ Diagnostics were made by a certified neurologist using NINCDS-ADRDA criteria (AD) and Peterson criteria (MCI). − Poor description of recruitment procedures. − No distinction between amnesic and non-amnesic MCI. −No measurement of AD-pathology biomarker (PET/CSF tau and amyloid-β).	+ Correction for intracranial volume and age.	+ Siemens 3.0 T MRI system. + T1-weighted MPRAGE images. − Manual segmentation. Targeted structures: the anterior olfactory nucleus, olfactory tubercle, piriform cortex, anterior portion of the periamygdaloid cortex and amygdala, and anterior perforated substance. + Same method for both groups.	AD: 15 MCI: 21 Controls: 27	AD; 71.9 (11.9) MCI: 73.2 (9) Controls: 69.5 (10.4)	MCI and AD patients had a significantly lower POC volume than controls. The difference between AD and MCI patients did not reach significance.

Note. AD: Alzheimer's disease, LMCI: Late mild cognitive impairment, EMCI: Early mild cognitive impairment, NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, MMSE: Mini-Mental State Examination, CVLT-II: The California Verbal Learning Test Two. * The data set was provided by the authors and has been used in both studies [78-79].

Indeed, three studies compared POC volumes between patients with AD and controls. Two studies found a significantly smaller volume in patients with AD, with one study reporting a more important decrease in the left POC for those with AD (Al-Otaibi et al., 2021). Among these three studies, two studies included MCI groups. Both studies found smaller POC volumes in patients with MCI compared to controls, but only one comparison was significant (Vasavada et al., 2015). One study compared patients with early MCI to those with late MCI and reported a smaller volume for the early MCI group (Lu et al., 2019).

Discussion

This meta-analysis and systematic review examined neuroanatomical structures involved in primary olfactory processing in both MCI and AD. We found a lower OB volume in both clinical groups compared to those in the control groups. When looking at the POC, despite the small number of the studies included in the present meta-analysis, a trend for lower volume is also found in both clinical groups compared to those in the control groups. These results are consistent with the hypothesis of a progressive atrophy of brain structures involved in olfactory processing in the course of AD. Volumetric reduction of olfactory brain structures is measurable as early as the MCI stage and is still more severe at the dementia stage.

The volumetric reductions in olfactory brain structures are in line with post-mortem studies that showed the presence of amyloid-β plaques and neurofibrillary tangles in both

OB and POC of patients with AD (Kovács et al., 1999; Tsuboi et al., 2003; Kovács et al., 2001). Kovács et al. (2001) demonstrated and argued that OB damage occurs very early in Braak's staging (i.e., stage 0 or I) before AD pathology spread through the central olfactory system. Our results regarding the volumetric reduction of OB and POC in patients with MCI or AD support this hypothesis. Volumetric reduction of these structures might have resulted from neurodegeneration due to the accumulation of amyloid-β plaques and neurofibrillary tangles (Jack et al., 2016). Thus, amyloid-β plaques and neurofibrillary tangles are hypothesized to cause early damage in OB and POC of patients with AD and could result in a volumetric reduction of these structures that is measurable from MRI scans. However, it is important to note that this meta-analysis and systematic review included studies based on clinical criteria for both AD and MCI rather than on specific neuropathological measurements of AD. Therefore, future studies should include measurements of AD-pathology, such as CSF amyloid-β, amyloid PET, CSF phosphorylated tau, and tau PET, in order to verify that damages to olfactory structures are the direct expression of AD pathology. This consideration is particularly important in studies involving MCI patients since it is only a portion of MCI patients that will convert to dementia (≈34%), and more specifically, ≈31% of MCI patients that will convert to Alzheimer dementia type (Hu et al., 2017).

Neurodegeneration could explain olfactory deficits found in AD. The disease affects main olfactory functions such as odor detection threshold, discrimination of different odors, with a more severe deficit in higher-order olfactory tasks such as identification and

recognition of odors (Rahayel et al., 2012). One study found that left hippocampus volume reduction is related to poorer olfactory identification, which requests both olfactory and memory abilities (Murphy et al., 2003). The current study shows that the volumetric reduction observed in the course of AD is not specific to hippocampal structures and is found in other brain structures related to olfactory functions, i.e., the OB and POC. OB volume was found to be related to some specific olfactory functions such as odor identification (Buschhüter et al., 2008) and odor detection threshold (Gudziol et al., 2009; Haehner et al., 2008). Thus, impaired performance of patients with AD on these functions might have resulted from neurodegeneration that occurred in OB. POC volume was also found to be related to some specific olfactory functions. One of the POC structures, the piriform cortex, is responsible for encoding odor objects (Gottfried, 2010). Deficits in olfactory functions such as odor identification were found to be strongly correlated with tau and amyloid deposition within this structure (Li et al., 2010; Macknin et al., 2004; Wesson et al., 2010). Another structure of the POC, the entorhinal cortex, seems to be involved in olfactory functions as this structure plays a role in the transmission of olfactory information to the hippocampus (Wilson et al., 2015; Staubli et al., 1984). However, the specific role of the entorhinal cortex in olfactory functions remains unclear, as very few studies have investigated this question. On a structural level, Petekkaya et al. (2020) showed a significant and positive correlation between the volume of the entorhinal cortex and the OB. On a behavioral level, Devanand et al. (2010) did not find any correlation between the entorhinal cortex volume and scores of odor identification. More behavioral and neuroimaging studies are needed to better understand the role of these structures and

to better qualify the consequences of OB and POC volume reduction on olfactory functions in AD.

From a clinical point of view, neuroimaging techniques allow the quantification of brain structures and thus provide the possibility to detect in vivo cerebral atrophy, which can be used as a marker of neurodegeneration. Our results suggest that a volume reduction of OB and POC can be observed early in the course of the disease and can be detected from the MCI stage. Thus, OB and POC volume reduction might be new interesting biomarkers of AD. However, olfactory dysfunctions and atrophies in olfactory-related structures are not specific to AD and are also present in other neurodegenerative diseases such as Parkinson's disease (Wang et al., 2011). Therefore, we propose to combine OB and POC volume reduction with more traditional biomarkers such as hippocampal atrophy to enhance the specificity of the early diagnosis of AD. As a result, using this new combining approach, we might increase the detection of those with MCI that will convert to AD.

At a methodological level, although we found a global effect size in favor of an OB volume reduction of patients with AD compared to healthy older controls, it was statistically heterogeneous. When analyzing the clinical and methodological diversity among studies, they were all very similar. Since our research question was precise and because the studies included in the meta-analysis shared many similarities, we concluded that the combination of different effects sizes was appropriate. The small number of

studies included (n = 6) prevented us from conducting moderator analysis, which is what is recommended when heterogeneous effect sizes are found (Hedges & Olkin, 2014). Factors such as the hardware/software used, the type of scanner or sequence used to measure the OB volume could explain such heterogeneity (Potvin et al., 2019; Reig et al., 2009). OB volume is also known to have a large interindividual variability and this variability could also explain the heterogeneity (Kovács et al., 2001). Another factor that could explain heterogeneity is that not all studies controlled for total intracranial volume, which is an important covariate to take into consideration when analyzing volumetric data. Finally, heterogeneity could be explained by the fact that the majority of studies included used a manual segmentation technique instead of an automatic segmentation technique to obtained OB volumetric data. Futures studies should focus on the development of automatic segmentation methods of the OB (Noothout et al., 2021).

This meta-analysis and systematic review have certain limitations. The most apparent is the small number of studies included. In fact, one of the main results of this study is that there is a lack of scientific literature for studies that have examined brain structures related to olfactory functions in the course of AD. Therefore, with only four studies resulting from the systematic review process that compared POC or OB volume between patients with MCI and healthy elderly controls, we were unable to conduct a meta-analysis using a random-effects model, as is typically recommended (Jackson & Turner, 2017). Regarding the selection bias of the studies included in the reviews, we were unable to evaluate the quality of two studies (Zeng et al., 2015; Hang et al., 2014) as only the title and abstracts

were written in English (full texts were in Chinese and we received no response from the authors). However, we decided to include these two studies in the meta-analysis, since all pertinent information was accessible in the abstracts and the studies were published in peer-reviewed journals. For all the included studies except the last two, we used the NOS tool to assess the risk of bias as recommended (Peterson et al., 2011). No studies were excluded following the risk of bias assessment. Finally, a close examination of the included studies showed some divergence on the structures included in the POC. Several models of the POC have been conceptualized (Fjaeldstad et al., 2017; Wang et al., 2010; Seubert et al., 2013), but they generally included common structures such as the piriform cortex, the anterior olfactory nucleus, the amygdala, the periamygdaloid cortex, and the anterior performed substance. Nevertheless, there is a need for a better classification of the structures included in the POC, especially if POC volume is used as an early biomarker of AD.

Our results indicate a volumetric reduction of both OB and POC in patients with AD and results of studies from the systematic review show that this reduction is also present in patients with MCI. New studies are needed to better characterize the degree of volume reduction of both OB and POC in patients with MCI or those that are in an earlier stage of the disease, for instance those with a SCD (Jessen et al., 2014). Second, no studies included the distinction between amnesic and non-amnesic MCI groups. Future studies should compare olfactory structures between these subgroups since amnesic MCI has been associated with a greater olfactory impairment compared to non-amnesic MCI patients

(Park et al., 2018). Third, there is a need to encourage longitudinal studies that focus on volume reduction of olfactory-related structures in the course of AD. Results from these studies could support the hypothesis that the volume of neuroanatomical structures involved in olfactory processing decrease as the disease progresses. Longitudinal studies with larger samples of cognitively healthy participants at baseline could also lead to the analysis of the predictive value of these volumetric measurements on the development of AD-related cognitive and olfactory decline. Lastly, future researches should focus on a better characterization of the POC and on the development of fully automatized segmentation methods of these structures.

Conclusions

To conclude, a volumetric reduction of the neuroanatomical structures involved in olfactory functioning is present in patients with AD and can be measured as early as the MCI stage. Combining this neuroanatomical finding with more traditional biomarkers of AD, such as the hippocampal atrophy, volumetric reduction of OB and POC could increase the specificity of the early diagnosis of AD.

Author Contributions

B.J.: Data curation; formal analysis; investigation; methodology, project administration; visualisation; writing—original draft. B.B.: Conceptualization; methodology, funding acquisition; resources, supervision; writing—review & editing. J.F.: Conceptualization; funding acquisition; resources, methodology, supervision,

writing—review & editing. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

Since this study is a meta-analysis and a systemic review of the scientific literature, the study did not report data that were not already available.

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Conflicts of Interest

The authors declare no conflict of interest.

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Article scientifique 2

Smaller grey mattr volume in the central olfactory system in mild cognitive impairment

Smaller grey matter volume in the central olfactory system in mild cognitive impairment[1]

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Abstract

One of the major challenges in the diagnosis of Alzheimer's disease (AD) is to increase the specificity of the early diagnosis. While episodic memory impairment is a sensitive AD marker, other measures are needed to improve diagnostic specificity. A promising biomarker might be a cerebral atrophy of the central olfactory processing areas in the early stages of the disease since an impairment of olfactory identification is present at the clinical stage of AD. Our goal was therefore, (1) to evaluate the grey matter volume (GMV) of central olfactory processing regions in prodromal AD, and (2) to assess its association with episodic memory. We included 34 cognitively normal healthy controls (HC), 92 individuals with subjective cognitive decline (SCD), and 40 with mild cognitive impairment (MCI). We performed regions of interest analysis (ROI) using two different approaches, allowing to extract GMV from (1) atlas-based anatomical ROIs, and from (2) functional and non-functional subregions of these ROIs (¬olfactory ROIs and non-olfactory ROIs). Participants with MCI exhibited smaller olfactory ROIs GMV, including significant reductions in the piriform cortex, amygdala, entorhinal cortex, and left hippocampus compared to other groups ($p \leq 0.05$, corrected). No significant effect was found regarding anatomical or non-olfactory ROIs GMV. The left hippocampus olfactory ROI GMV was correlated with episodic memory performance ($p < 0.05$ corrected). Limbic/medial-temporal olfactory processing areas are specifically atrophied at the MCI stage, and the degree of atrophy might predict cognitive decline in AD early stages.

Keywords: Olfactory Cortex, Volumetry, Mild Cognitive Impairment, Subjective Cognitive Decline, MRI, episodic memory.

Highlights

- Prior activated areas in fMRI studies determined olfactory processing ROIs.
- Grey matter volume of olfactory areas is reduced in mild cognitive impairment.
- Neurodegeneration is focused on limbic and medial-temporal olfactory areas.
- Volume of central olfactory areas correlates with episodic memory performance.

Introduction

Alzheimer's disease (AD) begins with a silent phase that spans over decades, during which an accumulation of neurofibrillary tau and β-amyloid depositions lead progressively to dementia. On the neuropathological level, tau tangles spread to the trans-entorhinal regions, then to the limbic regions, before expanding to the neocortex (Braak & Braak, 1991). β-amyloid plaques, on the other hand, accumulate first in the neocortex, then in the allocortex regions such as the entorhinal cortex and the hippocampus, then in subcortical nuclei, the brainstem, and finally in the pons and the cerebellum (Thal et al., 2002). These neuropathologies also correlate with other underlying molecular damages such as caspase activation, which is another factor leading to neuronal death (Rohn et al., 2001). These brain damages occur during a prodromal phase in which the patient typically develops progressively a subjective cognitive decline (SCD) – a preclinical stage in which individuals report complaints of subjective cognitive decline while maintaining normal performance on clinical cognitive assessments (Jessen et al., 2014, 2020). Then, the progression of the disease leads to mild cognitive impairment (MCI), typically including an episodic memory deficit, before leading to dementia, at which point the cognitive

impairment is significant enough to impact daily life functionally (Albert et al., 2011; Jack et al., 2018; Sperling et al., 2011).

The amnesic form of MCI is considered a risk factor for developing AD dementia (Petersen et al., 2001). Among neuropsychological tests, performance on verbal episodic memory measures is the most accurate to predict the progression from MCI to AD dementia type (Belleville et al., 2017). Nevertheless, episodic memory impairment is not specific to AD, and a significant proportion of patients with an amnesic MCI will not convert to AD dementia type (Vos et al., 2013). As an example, results from a study showed that 31% of patients diagnosed with amnesic MCI did not convert to dementia after six years of follow-up (Mauri et al., 2012).

Combining episodic memory decline with other behavioral markers may improve the early detection of AD; for this, olfactory impairment is a prime candidate. During the prodromal phase of AD, olfactory decline appears among the first behavioral symptoms within the disease progression (Murphy, 2019). Indeed, olfactory impairment is a clinical symptom of AD (Mesholam et al., 1998; Rahayel et al., 2012; Silva et al., 2018; Velayudhan, 2015; Velayudhan et al., 2013) and is already present as episodic memory impairment appears at the MCI stage of the disease (Bahar-Fuchs et al., 2010; Devanand et al., 2010; Djordjevic et al., 2008; Eibenstein et al., 2005; Jung et al., 2019; Roalf et al., 2017; Seligman et al., 2013; Vyhnalek et al., 2015). While episodic memory and olfactory identification are associated during aging (Chen et al., 2018; Devanand et al., 2010; Jobin

et al., 2023; Larsson et al., 2016; Tonacci et al., 2017; Wehling et al., 2010), the olfactory decline may begin even before the appearance of memory deficits. Indeed, individuals with SCD can exhibit reduced olfactory identification abilities (Chen et al., 2021; Sohrabi et al., 2009) although memory impairments are per definition absent in this group. Further, in cognitively normal older adults, olfactory performance helps to predict future cognitive decline (Devanand et al., 2015; Dintica et al., 2019; Growdon et al., 2015; Olofsson et al., 2020; Sohrabi et al., 2012; Windon et al., 2019) and conversion to MCI (Roberts et al., 2016; Wheeler & Murphy, 2021; Wilson et al., 2007). Accordingly, olfactory impairment is considered a preclinical marker of AD.

In contrast to the olfactory impairment associated with other conditions such as Parkinson's disease, olfactory impairment within AD is characterized by a particular pattern where olfactory identification is more impaired than olfactory threshold or olfactory discrimination (Rahayel et al., 2012). This pattern can already be observed in MCI (Roalf et al., 2017). Such early olfactory identification impairment could result from damage to limbic and medial temporal lobe structures, as these regions are mainly involved in the identification of odors (Devanand et al., 2010; Hagemeier et al., 2016; Kjelvik et al., 2014, 2021; Kose et al., 2021; Murphy et al., 2003; Patin & Pause, 2015; Yoshii et al., 2019; Yu et al., 2019). Pathologically, tau tangles accumulate first in the trans-entorhinal region (Braak & Braak, 1991); tau accumulation is one of the leading causes of neuronal death and a predictor of brain atrophy in AD (Malpetti et al., 2022; Planche et al., 2022). Although the olfactory bulb is also affected by tau pathology in early

Braak stages (Kovacs et al., 1999), a post-mortem histological study showed that olfactory bulb tau pathology failed to predict olfactory identification (Tremblay et al., 2022), while other studies showed that olfactory identification would be associated with cerebrospinal fluid (CSF) tau pathology (Lafaille-Magnan et al., 2017; Reijs et al., 2017; Tu et al., 2020) and with tau pathology within medial-temporal lobe regions (Klein et al., 2021; Risacher et al., 2017). Accordingly, limbic and medial-temporal structures of the primary olfactory cortex (POC), which includes the piriform cortex, the amygdala, the olfactory nucleus, the olfactory tubercle, and the entorhinal cortex, are atrophied in patients with AD, raising the hypothesis that POC atrophy may be present as early as the MCI stage and being one of the main causes of the early olfactory identification impairment (Jobin et al., 2021a).

While several regions are involved in central olfactory processing (e.g., amygdala, piriform cortex, entorhinal cortex, parahippocampal gyrus, orbitofrontal cortex, insula, caudate, hippocampus, cingulate; Lundström et al., 2011; Seubert et al., 2013; Torske et al., 2021), neuropathological and behavioral evidence suggests that damage to limbic and medial-temporal olfactory regions is the first to appear during AD. Over time, odor identification and episodic memory have the same trajectories within aging (Dindica et al., 2021). According to the common cause hypothesis, damages to shared limbic and medial-temporal regions involved in both capacities would explain the relationship and similar trajectories between memory and olfactory declines in aging (Baltes & Lindenberger, 1997; Dulay & Murphy, 2002).

In the present study, we aimed to (1) compare and characterize grey matter volume (GMV) of the central olfactory structures of three groups, namely a control group of cognitively normal healthy older adults without cognitive complaints (HC), a group of older adults with SCD, and a group of older adults with MCI. Compared to cognitively normal controls, we hypothesized that older adults with SCD or MCI have smaller GMV of olfactory structures in the limbic system and medial-temporal lobe. We also aimed to compare the GMV of subregions of these structures across the three groups. Accordingly, we aimed to compare (2a) the olfactory subregions of these structures, i.e., areas that are activated during olfactory stimulation, and (2b) the non-olfactory subregions of these structures, i.e., areas that do not activate to olfactory stimulation, among the three groups. Here, we also predicted smaller GMV in olfactory subregions of these structures in SCD or MCI groups compared to HC participants. Finally, we aimed to (3) determine if the GMV of central olfactory areas is correlated to verbal episodic memory performance, the most accurate cognitive predictor of AD (Belleville et al., 2017). We hypothesized that GMV of olfactory medial temporal and limbic regions correlates with verbal episodic memory performance.

Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the research center of the Institut universitaire de gériatrie de Montréal. After a detailed explanation of the study, all participants provided written consent before enrolling in the study.

Participants

The data were obtained from the Consortium for the Early Identification of Alzheimer's Disease-Quebec (CIMA-Q, Belleville et al., 2019), established in 2013 with initial FRQS-Pfizer funding. The primary objective of CIMA-Q was to establish a cohort of older adults characterized clinically, cognitively, and by neuroimaging and blood sampling, with the following goals: (1) to establish an early diagnosis of Alzheimer's disease, (2) to make a well-characterized cohort available to the scientific community, and (3) to identify novel therapeutic targets to prevent or slow cognitive decline and Alzheimer's disease (4) via subsequent clinical studies. The designated principal investigator and director of CIMA-Q is Dr. Sylvie Belleville from the Research Centre of the Institut universitaire de gériatrie de Montréal, a research organization of the Centre Intégré Universitaire de Santé et de Services Sociaux du Centre-sud-de-l'île de Montréal. CIMA-Q represents the joint efforts of many Quebec-based co-principal investigators and researchers affiliated with Université Laval, McGill University, Université de Montréal, and Université de Sherbrooke.

Since 2014, CIMA-Q has recruited a longitudinal cohort of 350 cognitively normal participants, with SCD, with MCI, or with Alzheimer's type dementia. In the current study, we included all eligible participants who underwent MRI examination between 2014 and March 2020 (n = 166). All participants were community-dwelling older adults aged 65 or over, living independently from Montreal, Sherbrooke, and Quebec City in Canada. All participants underwent a complete comprehensive neuropsychological

evaluation and were evaluated by expert physicians who classified participants across the AD spectrum, from cognitively normal HC to SCD, MCI, and clinically probable AD.

All recruitment procedures, clinical, cognitive, and neuropsychiatric measurement, as well as all inclusion and exclusion criteria, were described (Belleville et al., 2019). Participants from the MCI group (Montreal Cognitive Assessment, MoCA, Nasreddine et al., 2005, score between 26 and 20) met the National Institute on Aging and the Alzheimer's Association (NIA-AA) clinical criteria for MCI (Albert et al., 2011): (1) a reported cognitive decline; (2) an objective cognitive impairment typically in episodic memory, (3) the preservation of independence in functional abilities, and (4) the absence of dementia. Participants from the SCD group (MoCA score ≥ 26) met the criteria of the Subjective Cognitive Decline Initiative (Jessen et al., 2014): (1) a reported cognitive decline, and (2) cognitive performance within the normal range. Cognitively normal controls participants (MoCA score ≥ 26) (1) reported no cognitive complaint, and (2) had a cognitive performance within the normal range. Verbal episodic memory performance measured by the Logical Memory II subtest of the Wechsler Memory Scale (Wechsler, 1997) and general cognitive performance measured by the MoCA are presented in Table 1.

Table 1.

Characteristics of Participants in Each Group

				p Values		
	HC (*n* = 34)	SCD (*n* = 92)	MCI (*n* = 40)	HC vs.SCD	HC vs. MCI	SCD vs. MCI
Age in years	72.08 (5.51)	72.18 (4.76)	75.22 (5.11)	.93	.008*	.002*
Female/Male	25/9	63/29	18/22	.58	.013	.011
Years of Education	15.88 (3.69)	15.05 (3.09)	14.30 (3.12)	n.a.	n.a.	n.a.
Logical Memory II delayed free recall	14.74 (4.67)	14.20 (3.86)	10.13 (4.42)	.52	< 0.001*	< 0.001*
MoCA	28.35 (1.37)	27.66 (1.41)	24.52 (2.34)	0.04	< 0.001*	< 0.001*
Memoria, free word recall[a]	8.18 (1.87)	7.33 (2.10)	6.07 (2.56)	0.055	< 0.001*	0.009*
Face-Name Test, delayed free recall[b]	5.35 (1.77)	4.68 (2.43)	2.95 (2.31)	0.15	< 0.001*	< 0.001*
Piriform cortex anatomical ROI	0.00123 (0.00010)	0.00123 (0.00010)	0.00116 (0.00009)	n.a.	n.a.	n.a.
Piriform cortex olfactory ROI	0.00066 (0.00006)	0.00066 (0.00006)	0.00062 (0.00006)	0.79	0.018*	0.002*
Piriform cortex non-olfactory ROI	0.00057 (0.00005)	0.00057 (0.00005)	0.00054 (0.00005)	n.a.	n.a.	n.a.
Amygdala anatomical ROI	0.00120 (0.00009)	0.00121 (0.00011)	0.00111 (0.00014)	n.a.	n.a.	n.a.
Amygdala olfactory ROI	0.00099 (0.00009)	0.00098 (0.00009)	0.00091 (0.0001)	0.82	0.014*	0.001*
Amygdala non-olfactory ROI	0.00021 (0.00005)	0.00022 (0.00003)	0.00020 (0.00003)	n.a.	n.a.	n.a.
Entorhinal cortex anatomical ROI	0.00275 (0.00025)	0.00273 (0.00028)	0.00257 (0.00033)	n.a.	n.a.	n.a.
Entorhinal cortex olfactory ROI	0.00098 (0.00010)	0.00097 (0.00010)	0.00090 (0.00011)	0.92	0.008*	.002*
Entorhinal cortex non-olfactory ROI	0.00177 (0.00018)	0.00176 (0.00020)	0.00167 (0.00022)	n.a.	n.a.	n.a.
Left hippocampus anatomical ROI	0.00203 (0.00016)	0.00203 (0.00018)	0.00186 (0.00026)	n.a.	n.a.	n.a.
Left hippocampus olfactory ROI	0.00007 (0.000009)	0.00007 (0.000009)	0.00006 (0.00001)	0.60	0.007*	0.006*
Left hippocampus non-olfactory ROI	0.00196 (0.00016)	0.00196 (0.00018)	0.00180 (0.00026)	n.a.	n.a.	n.a.
Left parahippocampal gyrus anatomical ROI	0.00209 (0.00019)	0.00205 (0.00016)	0.00196 (0.00018)	n.a.	n.a.	n.a.
Left parahippocampal gyrus olfactory ROI	0.00002 (0.000003)	0.00002 (0.000004)	0.00002 (0.000005)	0.89	0.01*	0.004*
Left parahippocampal gyrus non-olfactory ROI	0.00207 (0.00019)	0.00203 (0.00016)	0.00193 (0.00018)	n.a.	n.a.	n.a.
Insula anatomical ROI	0.00750 (0.00060)	0.00757 (0.00060)	0.00728 (0.00066)	n.a.	n.a.	n.a.
Insula olfactory ROI	0.00053 (0.00005)	0.00054 (0.00005)	0.00053 (0.00006)	0.80	0.77	0.94
Insula non-olfactory ROI	0.00696 (0.00055)	0.00703 (0.00058)	0.00675 (0.00062)	n.a.	n.a.	n.a.

Table 1.

Characteristics of Participants in Each Group (continued)

				p Values		
	HC (*n* = 34)	SCD (*n* = 92)	MCI (*n* = 40)	HC vs. SCD	HC vs. MCI	SCD vs. MCI
Orbitofrontal anatomical ROI	0.00810 (0.00046)	0.00800 (0.00064)	0.00780 (0.00055)	n.a.	n.a.	n.a.
Orbitofrontal olfactory ROI	0.00030 (0.00003)	0.00029 (0.00004)	0.00027 (0.00003)	0.24	0.50	0.04
Orbitofrontal non-olfactory ROI	0.00781 (0.00044)	0.00772 (0.00061)	0.00751 (0.00052)	n.a.	n.a.	n.a.
Left caudate anatomical ROI	0.00177 (0.00018)	0.00123 (0.00009)	0.00116 (0.00009)	n.a.	n.a.	n.a.
Left caudate olfactory ROI	0.000002 (0.0000008)	0.000002 (0.0000009)	0.000002 (0.0000007)	0.46	0.07	0.15
Left caudate non-olfactory ROI	0.00176 (0.00018)	0.00183 (0.00024)	0.00174 (0.00025)	n.a.	n.a.	n.a.

Note. Values are means (SD). Analysis of variance was performed, followed by post-hoc pairwise comparisons with Holm-Bonferroni correction. A Chi-Square test of independence was performed for sex. Volumetric data represent volumes in mL divided by total intracranial volume. Volumetric analyses of variance were also performed, followed by post-hoc ANCOVAs controlling for age with Holm-Bonferroni correction. Abbreviations: HC = cognitively normal healthy controls, SCD = subjective cognitive decline, MCI = mild cognitive impairment. MoCA = Montreal Cognitive Assessment. n.a. = No post-hoc performed when the main group effect was non-significant. a Data missing for two subjects. b Data missing for four subjects. * indicates statistically significant effects after adjustment for multiple comparisons (Holm-Bonferroni corrected).

Design

The CIMA-Q project is a large-scale, multicenter, and longitudinal study including standardized cognitive and neuroimaging assessments (http://www.cima-q.ca/ for more details). After a telephonic pre-screening interview using the Mini-Mental State Examination (t-MMSE; Newkirk et al., 2004), all eligible participants underwent a clinical examination, a neuropsychological assessment, and a neuroanatomical MRI scan. MRI assessments were completed within a maximum of 30 days after the cognitive

examination. All measurements from this study have been collected before the COVID-19 pandemic.

Episodic Memory Assessment

To reduce circularity issues when testing our hypothesis, we chose a different episodic memory task than those used in the inclusion criteria. Specifically, we used performance at a free word recall task from the Memoria Word Recall test (Chatelois et al., 1993). During the procedure, a 15-word list was presented to the participant on a computer screen displayed in a matrix of 5 rows and 3 columns. After the instructor verbally indicated the word to point on the screen, the participant had to point with his finger the word to remember for subsequent recall. This procedure was repeated 15 times for each word to learn, and for each item, words presentation on the screen was randomized to prevent spatial strategies during encoding. After the 15th word, participants were asked to count upwards to prevent rehearsal and to clear their working memory. Then, the participant was asked to retrieve as many words as possible previously seen during the learning phase. This task is among the most sensitive predictors of progression from MCI to dementia (Belleville et al., 2017).

Image Processing

CIMA-Q used a comprehensive imaging protocol harmonized for manufacturer/software configurations to ensure optimal convergence during analysis

(Belleville et al., 2019; Duchesne et al., 2019). In this study, we used anatomical 3D-T1-weighted sequences from this protocol.

We converted all 3D T1-weighted MR images into the Neuroimaging Informatics Technology Initiative (NIFTI) format, and we manually reoriented the anterior commissure as the origin for all images. The images were spatially normalized and segmented into grey matter (GM), white matter (WM), and cerebral spinal fluid (CSF) tissue classes according to the Geodesic Shooting registration approach with default settings in 1.5 mm cubic resolution and MNI space using the CAT12 toolbox (Gaser et al., 2022) implemented in SPM12 (Wellcome Centre of Imaging Neuroscience, Institute of Neurology, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm) and MATLAB software version R2020b (The MathWorks, Natick, MA, USA). GM, WM, and CFS Volumes were summed up to calculate the total intracranial volume (TIV). Moreover, the data quality was obtained from CAT12, and all scans were rated C+ or higher, representing a satisfactory quality level (Gaser et al., 2022). Regarding data quality, an ANOVA revealed no difference between groups regarding the weighted overall image quality (F[2, 165] = .67; p = 0.51).

GMV Extraction

We extracted GMV from regions of interest (ROIs) using the "Estimate Mean Values Inside ROI for External Analysis" CAT12's tool and performed analysis using SPSS software (IBM SPSS Statistics Version 28). We defined ROIs based on a recent activation

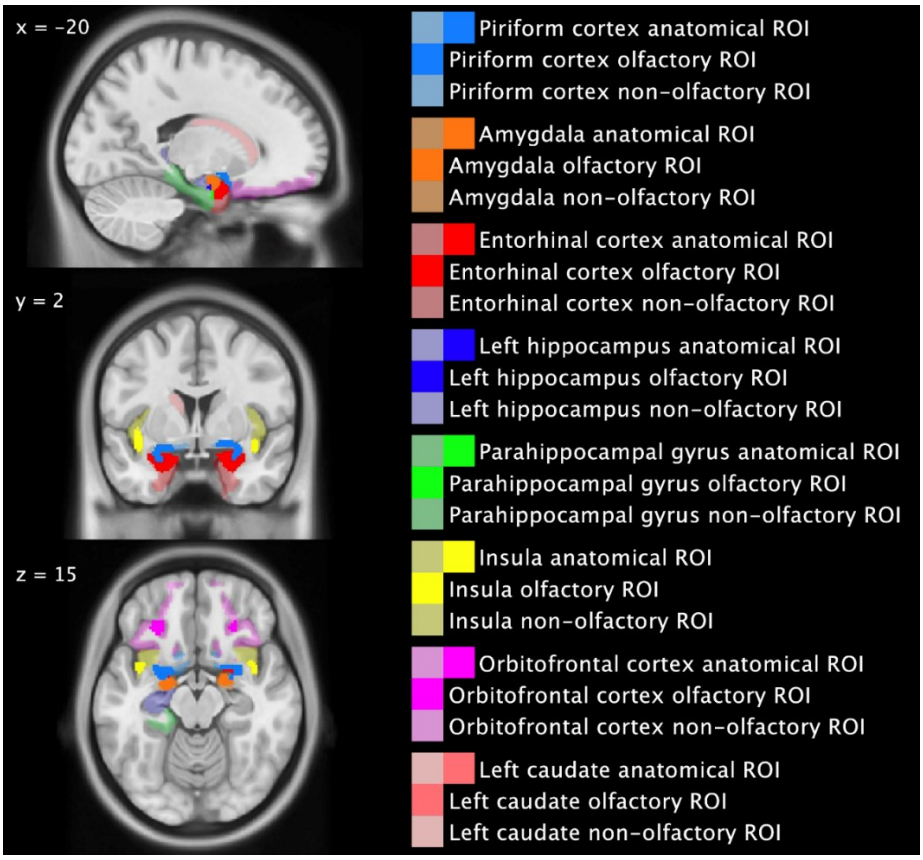
likelihood estimation (ALE) meta-analysis of 81 studies (Torske et al., 2021), a method previously used by Seubert et al. (2013). The activation mask resulting from this meta-analysis represents significant clusters that are activated during olfactory stimulation, providing a probabilistic map of the central olfactory system (i.e, the amygdala, piriform cortex, medial+posterior orbitofrontal cortex gyrus, insula, left parahippocampal gyrus, left hippocampus, and left caudate). For these last three regions, we were only able to extract the left hemisphere part given the absence of activation in the right hemisphere within these regions in the functional mask (Torske et al., 2021), a similar lateralization effect has been found in Fjaeldstad et al. (2021) regarding the structural connectivity between the olfactory cortex and the left hippocampus (VS the right hippocampus).

ROIs masks were created using an approach combining a functional mask (Torske et al., 2021) and a neuroanatomical atlas (Neuromorphometrics), a technique that has been used in other studies to create ROIs of the central olfactory system (Fjaeldstad et al., 2017, 2021; Postma et al., 2021). Since the piriform cortex is not included in the Neuromorphometrics atlas, we used a mask created by Zhou et al. (2019) which includes the anterior olfactory nucleus, olfactory tubercle, and piriform cortex. First, we extracted GMV from (A) ***anatomical ROIs*** (i.e., all voxels from different ROIs, based on the anatomical atlas masks). Second, we extracted GMV from another set of ROIs derived on the intersection between the functional mask (Torske et al., 2021) and anatomical regions from the Neuromorphometrics atlas included in CAT12 that is resulting from the OASIS project (http://www.oasis-brains.org/). These (B) ***olfactory ROIs*** included significant

voxels activated by olfactory stimulation from the anatomical ROIs masks. Thus, these novel ROIs represented the parts of anatomical atlas-based regions that are activated during olfactory stimulation (see Figure 1). Finally, we also extracted (C) ***non-olfactory ROIs*** GMV (i.e., voxels that are not activated during olfactory stimulation from the same anatomical regions). All GMV extracted were divided by the TIV to control for head size and reported in mL.

Figure 1.

Defined ROIs Used to Extract GMV from Different ROIs



Note. Anatomical ROIs were defined based on the Neuromorphometrics atlas implemented in CAT12 and the piriform cortex mask from Zhou et al. (2019). Olfactory ROIs represent significant voxels activated by olfactory stimulation (Torske et al., 2021) within each anatomical ROI. Non-olfactory ROIs represent voxels that are not activated during olfactory stimulation within each anatomical ROI. Axes' coordinates follow the MNI system.

Statistical Analysis

We used the same statistical analysis approach to compare each set of *ROIs* (*anatomical ROIs, olfactory ROIs, non-olfactory ROIs*) GMV between each group (HC, SCD, MCI). We computed Greenhouse-Geisser corrected repeated-measures analysis of variance (rmANOVA) with region (height levels: piriform cortex, amygdala, entorhinal cortex, left hippocampus, left parahippocampus, insula, orbitofrontal cortex, left caudate) as within-subject factor and group (three levels: HC, SCD, MCI) as between-subject factor. *Education, sex* and *age* were used as covariates. When an interaction effect between *region* and *group* was significant, we used ANCOVAs as post-hoc analysis to perform pairwise comparisons comparing GMV of each *ROI* between each group (HC VS SCD, HC VS MCI, SCD VS MCI) using age as a covariate. When an interaction effect between *region* and *sex* was significant, we performed two-way ANCOVAs that included *sex* and *group* (HC, SCD, MCI) as two factors, including age as a covariate. Pairwise comparisons were performed to compare GMV between males and females. Next, when an interaction effect was found between region and age, we performed Pearson's correlations to assess the relation between different *ROIs* GMV and *age*.

To assess the hemispheric laterality of different bilateral *ROIs* (piriform cortex, amygdala, entorhinal cortex, insula, orbitofrontal cortex), we performed the same analysis (Greenhouse-Geisser corrected rmANOVA), including *side* as a covariate.

We performed Pearson's correlations to verify the relationship between GMV of olfactory ROIs and age or episodic memory performance. Again, we set the alpha value at 0.05 and used Bonferroni-Holm correction for multiple comparisons. Partial correlation analysis was performed to control the effect of pertinent covariates (i.e., age).

Results

GMV of Anatomically Defined Regions (Anatomical ROIs)

When comparing GMV from *anatomical ROIs* between the three groups, a rmANOVA revealed no significant interaction between *region* and *group* (F[4.94, 395.26] = 0.867; p = 0.06; partial η^2 = .01), nor significant main effect of *group* (F[2, 160] = 2.76; p = 0.06; partial η^2 = .03). No significant interaction effects between *region* and *education* (F[2.47, 395.26] = 0.42; p = 0.70; partial η^2 = .003), nor main effect of education were found (F[1, 160] = 0.40; p = 0.84; partial η^2 > .001). We found a significant interaction between *region* and *age* (F[2.47, 395.26] = 3.05; p = 0.038; partial η^2 = .019). Age was significantly and negatively associated with each ROIs GMV (piriform cortex: r = -.25, p = 0.001); amygdala: r = -.33, p < 0.001; *entorhinal* cortex: r = -.25, p = 0.001; left hippocampus: r = -.41, p < 0.001), left parahippocampal gyrus (r = -.26, p < 0.001), insula (r = -.23, p = 0.003), orbitofrontal cortex (r = -.26, p < 0.001), and left caudate (r = -.24, p = 0.002) GMV.

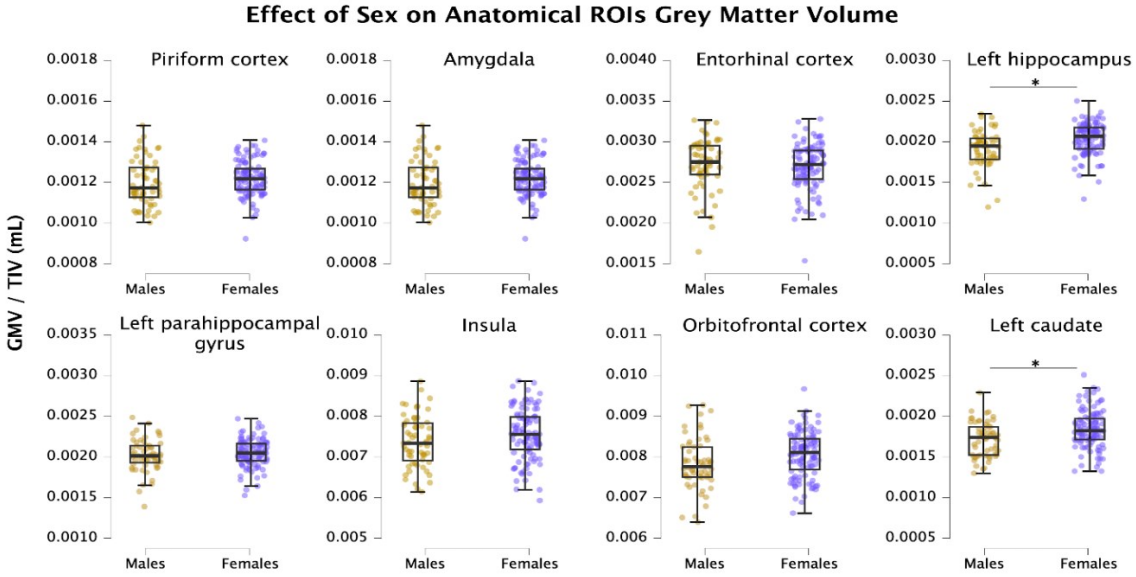
We also found an interaction effect between *region* and *sex* (F[2.47, 395.26] = 3.01; p = 0.036; partial η^2 = .019). Two-way ANCOVAs including *group* and *sex* as factors

showed significant main effects of *sex* for the left hippocampus ($F[1, 159] = 5.88$; $p = 0.02$; partial $\eta^2 = .036$). and for the left caudate ($F[1, 159] = 5.33$; $p = 0.02$; partial $\eta^2 = .032$). Post-hoc pairwise analysis revealed smaller left hippocampus ($p = 0.02$) and left caudate ($p = 0.02$) GMV in males compared to females (see Figure 2). No significant interaction effects were found between *group* and *sex* nor main effect of *sex* for other anatomical ROIs ($p > 0.05$).

Regarding laterality, we did not find a significant interaction effect between *region*, *group*, and *side* ($F[4.02, 321.24] = 0.59$; $p = 0.67$; partial $\eta^2 = .007$).

Figure 2.

Post-Hoc Two-Way ANCOVAs Comparisons Between Sex for Each Anatomical ROI, Controlled for Age



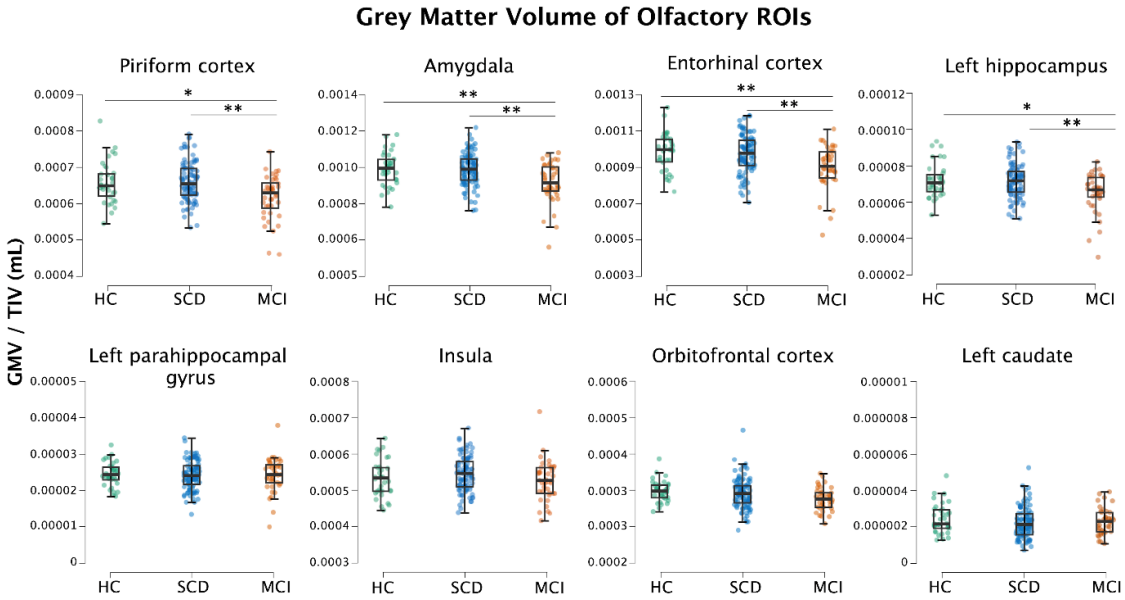
Note. Males exhibited significantly smaller GMV in the left hippocampus and left caudate compared to females. The boxes represent the interquartile range of GMV distributions, the middle lines represent the median. * indicates statistically significant differences at $p < 0.05$ that resisted to Holm-Bonferroni correction.

GMV of Olfactory Regions (Olfactory ROIs)

When comparing *olfactory ROIs* GMV between the three groups, the rmANOVA revealed a significant main effect of *group* (F[2, 160] = 5.02; p = 0.008; partial η^2 = .059) and *age* ([2, 160] = 9.76; p = 0.002; partial η^2 = .058), significant interactions between *region* and *group* (F[3,45, 275.73] = 4.01; p = 0.006; partial η^2 = .048), and significant interaction between *region* and *age* (F[1.72, 275.73] = 9.82; p > 0.001; partial η^2 = .058). No significant interaction effects between *region* and *sex* (F[1.72, 275.73] = 0.97; p = 0.37; partial η^2 = .006) or *education* (F[1.72, 275.73] = 0.44; p = 0.94; partial η^2 > .001) were found, nor main effect of *sex* (F[1, 160] = 0.47; p = 0.83; partial η^2 > .001) or *education* (F[1, 160] = 0.80; p = 0.78; partial η^2 = .001). Post-hoc ANCOVAs pairwise comparisons controlled for age revealed smaller GMVs in MCI compared to both SCD and HC in the piriform cortex, amygdala, entorhinal cortex, and the left hippocampus ($p \leq 0.05$), but not for the left parahippocampal gyrus, the insula, the orbitofrontal cortex, and the left caudate (p > 0.05) (see Figure 3).

Figure 3.

Post-Hoc ANCOVAs Pairwise Comparisons for Each Olfactory ROI Between the Three Groups (HC, SCD, MCI), Controlled for Age



Note. MCI group exhibited significantly smaller GMV in the piriform cortex, amygdala, entorhinal cortex, and left hippocampus compared to HC and SCD groups. The boxes represent the interquartile range of GMV distributions, the middle lines represent the median. p-values for each pairwise comparison: Piriform cortex: HC VS SCD $p = 0.82$, HC VS MCI $p = 0.014$, SCD VS MCI $p = 0.001$; Amygdala: HC VS SCD $p = 0.92$, HC VS MCI $p = 0.008$, SCD VS MCI $p = 0.002$; Entorhinal cortex: HC VS SCD $p = 0.60$, HC VS MCI $p = 0.007$, SCD VS MCI $p = 0.006$; Left hippocampus: HC VS SCD $p = 0.89$, HC VS MCI $p = 0.01$, SCD VS MCI $p = 0.004$; Left parahippocampal gyrus: HC VS SCD $p = 0.80$, HC VS MCI $p = 0.77$, SCD VS MCI $p = 0.94$; Insula: HC VS SCD $p = 0.24$, HC VS MCI $p = 0.49$, SCD VS MCI $p = 0.04$; Orbitofrontal cortex: HC VS SCD $p = 0.46$, HC VS MCI $p = 0.07$, SCD VS MCI $p = 0.15$; Left caudate: HC VS SCD $p = 0.20$, HC VS MCI $p = 0.59$, SCD VS MCI $p = 0.51$.

* indicates statistically significant difference at $p < 0.05$ that resisted to Holm-Bonferroni correction; ** indicates statistically significant difference at $p < 0.01$ that resisted to Holm-Bonferroni correction.

Regarding the interaction between *age* and *region*, linear Pearson's correlations showed that age was significantly and negatively associated with piriform cortex (r = -.26, $p < 0.001$), amygdala (r = -.35, $p < 0.001$), entorhinal cortex (r = -.27, $p < 0.001$), left hippocampus (r = -.22, $p = 0.005$), and orbitofrontal cortex (r = -.34, $p < 0.001$) GMV.

Regarding *olfactory ROIs* laterality, we did not find a significant interaction effect between *region*, *group*, and *side* (F[3.47, 277.51] = 1.06; $p = 0.37$; partial $\eta^2 = .01$).

GMV of Non-Olfactory Regions (Non-Olfactory ROIs)

In contrast, when comparing *non-olfactory ROIs* GMV between the three groups, a rmANOVA revealed no significant interaction between *region* and *group* (F[4.76, 380.63] = 0.87; $p = 0.49$; partial $\eta^2 = .011$), nor main effect of group (F[2, 161] = 2.21; $p = 0.11$; partial $\eta^2 = .027$). No significant interaction effects between *region* and *sex* (F[4.76, 380.63] = 0.87; $p = 0.50$; partial $\eta^2 = .017$) or *education* (F[2.40, 380.63] = 0.46; $p = 0.68$; partial $\eta^2 = .003$) were found, nor main effect of *sex* (F[1, 160] = 2.85; $p = 0.09$; partial $\eta^2 = .018$) or *education* (F[1, 160] = 0.03; $p = 0.86$; partial $\eta^2 > .001$). However, we found a significant interaction between *region* and *age* (F[2.38, 380.63] = 4.13; $p = 0.012$; partial $\eta^2 = .025$). Age was significantly and negatively associated with the entorhinal cortex (r = -.22, $p = 0.005$), left hippocampus (r = -.41, $p < 0.001$), left parahippocampal gyrus (r = -.27, $p < 0.001$), insula (r = -.24, $p = 0.002$), orbitofrontal cortex (r = -.25, $p = 0.001$), and left caudate (r = -.24, $p = 0.002$) GMV. Regarding

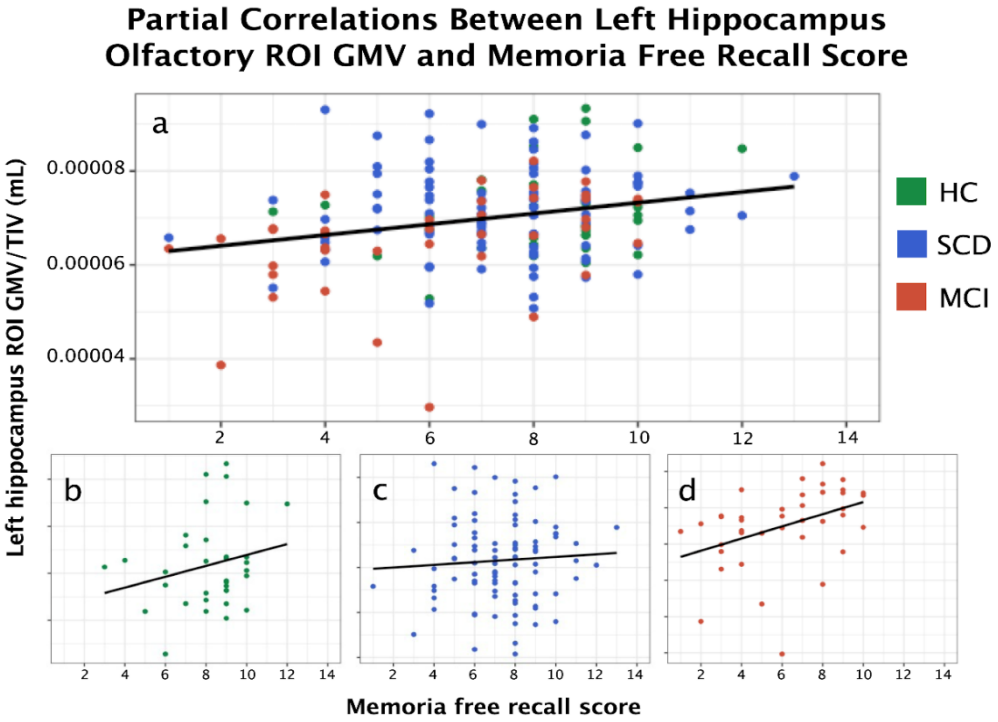
laterality, we did not find a significant interaction effect between *region*, *group*, and *side* ($p = 0.60$).

Relationship Between Olfactory ROIs GMV and Episodic Memory Performance

When analyzing the relationship between *olfactory ROIs'* GMV and episodic memory performance in the whole sample ($n = 166$), we observed significant linear correlations between Memoria free word recall scores and the piriform cortex ($r = .21$, $p = 0.007$), amygdala ($r = .25$, $p = 0.001$), and left hippocampus ($r = .26$, $p < 0.001$) GMV. After controlling for age using a partial correlation, only the left hippocampus GMV remained significantly correlated to episodic memory performance after correction ($r = .22$, $p = 0.005$). When analyzing the relationship between olfactory ROIs and episodic memory by groups (HC, SCD, MCI), no significant correlations were found between GMV and episodic memory, although there was a trend within the MCI group (HC: $r = .23$, $p = 0.20$; SCD: $r = .04$, $p = 0.74$; MCI: $r = .31$, $p = 0.056$) (see Figure 4).

Figure 4.

Partial Correlations Between Left Hippocampus Olfactory ROI and Memoria Free Recall Score



Note. a. represents a partial positive correlation ($r = .22$, $p = 0.005$) between left hippocampus olfactory ROI GMV and Memoria free recall score, controlling for age, for the whole sample. The three other panels represent the same analysis by group (b. HC, c. SCD, d. MCI respectively), without statistically significant effects (all $p > 0.05$).

When performing the same partial correlation analysis with *anatomical ROIs* and *non-olfactory ROIs*, we obtained the same pattern where only left hippocampus GMV remained significantly correlated to episodic memory performance after correction (*anatomical ROI:* $r = .30$, $p < 0.001$; *non-olfactory ROI:* $r = .29$, $p < 0.001$). When performing the analysis by groups (HC, SCD, MCI), we did not find any significant correlations were found between GMV and episodic memory ($p > 0.05$).

Discussion

In this study, we examined GMV of central olfactory structures and its relationship with episodic memory performance in individuals at risk of AD dementia. We found that GMV of piriform cortex, amygdala, entorhinal cortex, and left hippocampus olfactory subregions were smaller in the MCI group compared to both other groups. We also found that this neurodegenerative pattern is specific to olfactory processing areas since we did not find similar effects outside defined olfactory ROIs (*non-olfactory ROIs*) within the same regions, nor when using whole regions GMV (*anatomical ROIs).* Finally, the GMV of the left hippocampus ROIs correlated with episodic memory performance.

Consistent with previous reports (Chen et al., 2021; Jobin et al., 2021a; Lu et al., 2019; Vasavada et al., 2015), these results suggest that atrophy of central olfactory processing areas is present in individuals with MCI. More specifically, our data suggest a distinct and specific structural atrophy pattern where temporal-medial and limbic olfactory processing areas are damaged early in the prodromal stage of AD. This pattern is

consistent with the Braak staging of neurofibrillary changes, where tau tangles appear very early within trans-entorhinal and then in limbic regions before expanding to isocortical areas of the brain (Braak & Braak, 1991), supporting the hypothesis that olfactory impairment observed in prodromal AD reflects early neuronal damage caused by tau pathology in medial-temporal and limbic regions of the brain. Indeed, several studies have linked CSF and PET tau levels to olfactory performance in healthy older adults (Lafaille-Magnan et al., 2017; Risacher et al., 2017; Tu et al., 2020) and in mixed AD-continuum groups (Klein et al., 2021; Reijs et al., 2017).

The observed atrophy pattern of the central olfactory processing areas occurring first in the temporal-medial and limbic areas is also consistent with a newly proposed model (Planche et al., 2022) suggesting that atrophy progression in AD starts in (1) the hippocampus and amygdala; before progressing to (2) the middle temporal gyrus, (3) entorhinal cortex, parahippocampal cortex and other temporal areas, (4) striatum and thalamus, and (5) middle frontal, cingular, parietal and insular cortex. It is important to point out that Planche's model does not include the piriform cortex. However, given its anatomical and functional connections with the amygdala, entorhinal cortex, and hippocampus (Carmichael et al., 1994; Zhou et al., 2019, 2021), our observation of atrophied piriform cortex is in line with the model. These two models (Braak & Braak, 1991; Planche et al., 2022) demonstrated that key primary olfactory cortex structures are among the first to be damaged in AD.

Furthermore, damages to the olfactory system in AD could even be detected earlier, as recent studies showed that caspase activation, a molecular pathology that precedes and leads to tau-tangles (de Calignon et al., 2010), is present in the human anterior olfactory nucleus, is related to cognitive performance (Foveau et al., 2016), cooccurs with olfactory bulb atrophy, and is correlated to olfactory performance in Huntington's Disease murine model (Laroche et al., 2020; Lessard-Beaudoin et al., 2019). Future studies need to investigate caspase activation and its relationship to olfactory performance in AD models.

On a behavioral level, early atrophy of medial-temporal and limbic olfactory regions could explain why olfactory identification is early impaired during AD development (Rahayel et al., 2012; Roalf et al., 2017). Indeed, damage to medial-temporal and limbic olfactory regions is associated with a reduced olfactory identification performance, as smaller hippocampal volumes are related to worse olfactory identification performance in community-dwelling older adults (Devanand et al., 2010; Kose et al., 2021) and in patients with MCI or AD (Hagemeier et al., 2016; Kjelvik et al., 2014; Murphy et al., 2003; Yoshii et al., 2019; Yu et al., 2019). Although the amygdala has been associated with emotional processing and aversive stimuli (Patin & Pause, 2015), its volume is also linked to olfactory identification performance in older adults (Kose et al., 2021). Further, the primary olfactory cortex (including piriform cortex, amygdala, anterior olfactory nucleus, and olfactory tubercle) is smaller in AD and MCI compared to healthy older adults (Al-Otaibi et al., 2021; Vasavada et al., 2015) and the piriform cortex is less activated during an olfactory identification task in patients with amnesic MCI or AD (Kjelvik et al., 2021).

The olfactory orbital-frontal/insular regions are also activated during an odor identification task (Suzuki et al., 2001; Wang et al., 2005). Although we did not detect any significantly smaller volume in these regions, neuronal damage to the primary olfactory regions probably prevents the proper transmission of olfactory information to these regions, which would also impair olfactory identification performance. Indeed, previous work demonstrated that olfactory quality coding is already disrupted at the piriform cortex processing level and mediates olfactory deficits in AD (Li et al., 2010). Finally, the olfactory system impairment in neurodegenerative diseases is complex and damage to more peripheral olfactory structures such as the olfactory bulb or olfactory neuroepithelium could also contribute to olfactory impairment in AD. While neurofibrillary tangles are present in the first Braak's stages (0-1) in the olfactory bulbs (Kovacs et al., 2001) and the olfactory bulb volume is smaller in MCI patients (Jobin et al., 2021a), amyloid-β aggregates accumulate in the olfactory mucosa of MCI patients (Ayala-Grosso et al., 2015; Dibattista et al., 2020 for a review).

Our findings indicate that damage to the central olfactory system is first observable during the MCI stage of Alzheimer's disease. However, evidence suggests that sensory decline may begin before the onset of MCI. Older adults with SCD show a trend for worse olfactory identification performance compared to healthy controls (Jobin et al., 2021b). In the same vein, individuals with SCD or MCI exhibit reduced capacity to identify odors, combined with a reduced GMV of the bilateral hippocampus, bilateral parahippocampal gyrus, entorhinal cortex, right gyrus rectus, left caudate nucleus, and left putamen, and

reduced functional connectivity between left and right hippocampus compared to healthy older participants (Chen et al., 2021). In our study, we did not find any significant difference between SCD and HC groups regarding GMV of olfactory regions. This result may be due to the large heterogeneity of the SCD population and the lack of specificity of the SCD symptom to predict who will convert to AD in community-based cohorts (Slot et al., 2019). Longitudinal studies involving cognitively normal older adults positive to tau and β-amyloid biomarkers should verify whether olfactory decline, and its associated structural and functional damage, start before or at the same time as the onset of memory impairment. Future studies should also include participants from large and publicly available cohorts, such as the ADNI cohort, to replicate the cross-sectional results of this study.

Age was also independently significantly associated with piriform cortex, amygdala, entorhinal cortex, left hippocampus, and orbitofrontal cortex olfactory ROIs GVM. These relationships are unsurprising as olfaction declines with age (Doty & Kamath., 2014; Mackay-Sim et al., 2006; Oleszkiewicz et al., 2019). Interestingly, except for the orbitofrontal cortex, all these structures were also independently smaller in the MCI when controlling for age using post-hoc ANCOVAs, suggesting a more severe alteration in MCI that might be due to AD within the limbic/medial-temporal olfactory system.

Our results show that left hippocampus and left caudate *anatomical ROIs* were smaller in males compared to females. These results are consistent with previous reports

suggesting greater atrophy in males for temporal regions (Brun et al., 2009), the hippocampus (Jack et al., 2015; Murphy, 1996) in older adults, and the left caudate (Persson et al., 2018). Interestingly, males typically exhibit lower olfactory performance than females (Sorokowski et al., 2019), which may be explained by endocrine-related effects on brain regions involved in olfaction, including the hippocampus (Doty & Cameron, 2009). Indeed, sex hormones such as estrogen are neuroprotective for the hippocampus during adult life (Siddiqui et al., 2016; Zarate et al., 2017). Their reduction during menopause accelerates aging, which explains why females are more at risk of AD and decline to the dementia stage more quickly than males (Li & Singh., 2014; Yue et al., 2005).

After controlling for age, verbal episodic memory performance was correlated with the left hippocampus olfactory ROIs GMV. This significant correlation is not surprising since the left hippocampus is involved in both olfactory and memory functions (Gabrieli et al., 1997; Hummel et al., 2010; Kjelvik et al., 2021; Lundström et al., 2011; Squire & Zola, 1991, 1996; Zald & Pardo, 2000), and that episodic memory and olfactory functions are associated in the healthy older adult population (Chen et al., 2018; Devanand et al., 2010; Jobin et al., 2023; Larsson et al., 2016; Tonacci et al., 2017; Wehling et al., 2010). This could suggest an overlap between olfactory and memory functions within the left hippocampus, which would support the common cause hypothesis (Baltes & Lindenberger, 1997) suggesting that both sensory and cognitive declines related to aging stem from a shared factor—the deterioration of common cerebral structures. In line with

the common cause hypothesis, our results also support the hypothesis of a common trajectory of olfactory and memory decline within aging due to damages in shared medial-temporal regions (Dintica et al., 2021).

This study has certain limitations. The main limitation of this study is the lack of behavioral olfactory testing, which prevents the evaluation of the association between olfactory function and both structural and memory measures. Future studies should include olfactory measures, such as olfactory identification and olfactory threshold assessments. Another limitation is that most participants were recruited from the community, which are less impaired and less likely to convert to dementia than patients from memory clinics (Farias et al., 2009; Slot et al., 2019). This suggests that the observed effect may be even bigger amongst the clientele of memory clinics.

Conclusion

Limbic and medial-temporal olfactory processing areas are smaller in patients with MCI compared to participants with SCD and controls. Moreover, the olfactory processing area of the left hippocampus correlated with episodic memory performance, suggesting a potential overlap between olfactory and memory functions within this region.

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Conflict of Interest

The authors declare no conflict of interest.

CRediT Author Statement

B.J.: Data curation; formal analysis; investigation; methodology, project administration; visualisation; writing—original draft. B.B.: Conceptualization; funding acquisition; resources, methodology; supervision; writing—review & editing. J.F.: Conceptualization; funding acquisition; resources, methodology, supervision, writing—review & editing.

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Article scientifique 3

Olfactory Identification in Subjective Cognitive Decline: A Meta-Analysis

Olfactory Identification in Subjective Cognitive Decline: A Meta-Analysis[1]

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Abstract

Background: Recently, subjective cognitive decline (SCD) has been considered to be one of the first signs of Alzheimer's disease (AD). Since this potential early marker is sensitive but not specific to AD, combining it with other markers could ensure higher accuracy when predicting which persons with SCD will convert to AD. Since olfactory dysfunction is observable in both AD and mild cognitive impairment (MCI), it is a promising marker that could help improve the early diagnosis of AD. **Objective:** The aim of this meta-analysis was to verify whether the presence of SCD is associated with a decrease in olfactory identification ability. **Methods:** We collected articles from the following databases: PsychNet, PubMed, Ebsco, and ProQuest using the keywords: "SCD", "subjective cognitive decline", "subjective cognitive impairment", "subjective memory impairment", "subjective memory decline", "cognitive complaints", "memory complaints", "cognitive concerns", "memory concerns", "olfac*" and "smell". We included articles according to the following criteria: (1) participants aged 50 and over; (2) presence of an SCD group or a conceptual equivalent, (3) presence of a healthy control group with the same age range, and (4) assessment of olfactory identification ability. **Results:** Five studies met the inclusion criteria. Small and homogeneous effects were observed for olfactory identification alteration in individuals with SCD relative to controls (g = -0.16, 95% CI [–0.46, 0.14]). **Conclusion:** Despite the low number of studies included, the findings suggest that odor identification is slightly altered in SCD compared to healthy older adults. This alteration in individuals with SCD could be an early marker of AD.

Keywords: Alzheimer's disease, biomarker, meta-analysis, olfaction, olfactory identification, smell, subjective cognitive decline

Introduction

In 2017, approximately six million Americans were diagnosed with clinical Alzheimer's disease (AD) or mild cognitive impairment (MCI) due to AD pathology and this number is expected to rise up to 15 million by 2060 (Brookmeyer et al., 2018). AD is a neurodegenerative disease characterized by the accumulation of amyloid-ß plaques and tau neurofibrillary tangles in the brain that lead to dementia. Given the difficulty of measuring these brain markers in vivo, the probable diagnosis of AD is solely based on clinical criteria and usually occurs at the dementia stage (McKhann et al., 2011). However, AD has a long progression and begins with a preclinical phase, lasting decades, during which brain damage occurs (Jansen et al., 2015). This preclinical phase of AD ends with the development of MCI, which is characterized by cognitive impairments in one or more cognitive domains, most commonly in episodic memory in patients who will convert to AD dementia (Petersen, 2004; Albert et al., 2011). During the preclinical phase, the brain damage could express itself as subjective cognitive decline (SCD). SCD is subjective because, at this stage, the level of cognitive performance remains within normal range on classical clinical assessments (Jessen et al., 2014). Nevertheless, in individuals with SCD from the Consortium pour l'identification précoce de la maladie d'Alzheimer - Québec (CIMA-Q) cohort, hippocampal volume was linked to a decline in episodic memory performance, a relationship that was not present in healthy older adults (Caillaud et al.,

2019). However, although SCD is a sensitive marker for AD, it remains poorly specific. Not all cases of SCD will develop MCI or dementia (Jessen et al., 2020), and combining other earlier symptoms with SCD might be an opportunity to increase the specificity of the early diagnostic of AD. One potential sign is the olfactory dysfunction, which is a clinical marker of AD.

Several meta-analyses have shown that olfactory function is impaired in patients with AD, with the identification and recognition of odors being the more impaired functions (Rahayel et al., 2012; Silva et al., 2018). A similar impairment in the ability to identify odors was also found in MCI (Djordjevic et al., 2008; Lehrner et al., 2009; Peters et al., 2003; Roalf et al., 2017; Vasavada et al., 2017). Since MCI is considered as an early clinical stage of dementia (Albert et al., 2011), with a variable annual conversion rate from MCI to AD dementia of 7.5 to 16.5% (Ward et al., 2013), researchers have investigated the possible role of olfactory dysfunction as a predictor for the conversion from MCI to AD. Combined with other markers (informant report of functioning, verbal memory, hippocampal and entorhinal cortex volume), olfactory identification performance helped strongly predict conversion from MCI to AD after a 3-year follow-up (Devanand et al., 2008). In another study, MCI patients with pathological olfactory identification at baseline were more likely to develop dementia after a 2-year follow-up (Conti et al., 2013). When looking into different MCI subtypes, a population-based study showed that impaired olfactory identification was associated with amnestic MCI (aMCI) incidence, but not with non-amnestic MCI (naMCI) (Roberts et al., 2016). In the same study, olfactory

identification scores strongly predicted progression from aMCI to AD, which suggests that olfaction is more altered in aMCI than in naMCI and could be used as a marker of AD in MCI.

Longitudinal cohort studies on healthy community-dwelling older adults showed that olfactory dysfunction can predict cognitive decline. In cognitively healthy older adults, reduced olfactory function at baseline has been related to cognitive decline (Schubert et al., 2008; Swan & Carmelli, 2002), to a bigger proportion of conversion to MCI (Wilson, Schneider, Arnold, Tang, et al., 2007), and to a higher risk of developing dementia (Yaffe et al., 2017). Moreover, a longitudinal study including 1,037 cognitively healthy older adults at baseline showed that olfactory identification is a better predictor than verbal episodic memory to predict cognitive decline in the transition to MCI (Devanand et al., 2015). Overall, these findings suggest that olfaction could be an early marker for cognitive decline in the preclinical stages of AD. These findings are in line with Murphy's model (2019), which suggests that olfactory decline is one of the earliest clinical markers of AD, beginning at a stage when people are still cognitively within the norm, which might correspond to the SCD stage. Over the past decade, researchers have studied olfaction in SCD or a conceptually equivalent clinical entity. However, no consensus has been reached on whether the olfactory decline found in MCI and dementia is already detectable in this stage of the disease.

No meta-analyses have addressed olfaction in SCD. Thus, whether olfactory decline begins at the MCI stage or earlier remains unclear. The aim of this meta-analysis is to assess whether SCD is associated with a decrease in the ability of olfactory identification. In other words, we aim to address the following question: Do individuals with SCD have a reduced olfactory identification ability compared to healthy older adults?

Methods

The protocol of this meta-analysis was not registered.

Eligibility Criteria of the Studies Selected

To be eligible to be included in this meta-analysis, studies had to compare olfactory identification capacity between an SCD group and a healthy control group without cognitive complaint, with both groups comprising men and women aged 50 years and older.

Participants included in the SCD group had to report complaints of cognitive decline while having normal cognitive performance. There are two criteria to establish that an individual is experiencing a SCD: (1) subjective perception of cognitive decline relative to previous performance level, (2) a normal level of cognitive performance as assessed by valid cognitive tests such as the Mini-Mental State Examination (MMSE; Folstein et al., 1975), the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005), or other cognitive tests that are used to exclude MCI (Jessen et al., 2014). Thus, studies where

participants met both criteria of SCD were included in the meta-analysis. Given that the SCD term was only recently established in 2014 by the SCD-Initiative working group (Jessen et al., 2014) to describe individuals that are at risk of developing cognitive decline or dementia, and since memory complaint is the most frequent cognitive complaint reported, other terms such as subjective cognitive impairment, subjective memory complaint or subjective memory impairment were used to characterize these individuals. Thus, all studies assessing olfactory identification in individuals with cognitive complaint and normal scores on classical cognitive tests were included in the meta-analysis.

Participants in the control groups were healthy individuals of 50 years of age and over with no objective cognitive impairment (> –1.5 SD score on cognitive tests), as measured by a valid cognitive assessment, and did not self-report any complaints of cognitive decline. General exclusion criteria for both groups included: (1) being under 50 years of age, (2) presenting a cognitive impairment, and (3) having any psychiatric diagnosis or other neurological condition that could affect cognition.

Outcome

To be included in the meta-analysis, studies had to measure the sense of smell through a score obtained in a behavioral examination using validated olfactory identification tests such as the Sniffin' Sticks Identification Test (Hummel et al., 1997), the Odor Percept Identification Test (Tabert et al., 2005), the University of Pennsylvania Smell

Identification Test (UPSIT; Doty et al., 1984), and the Cross-Cultural Smell Identification Test (CC-SIT; Doty et al., 1996).

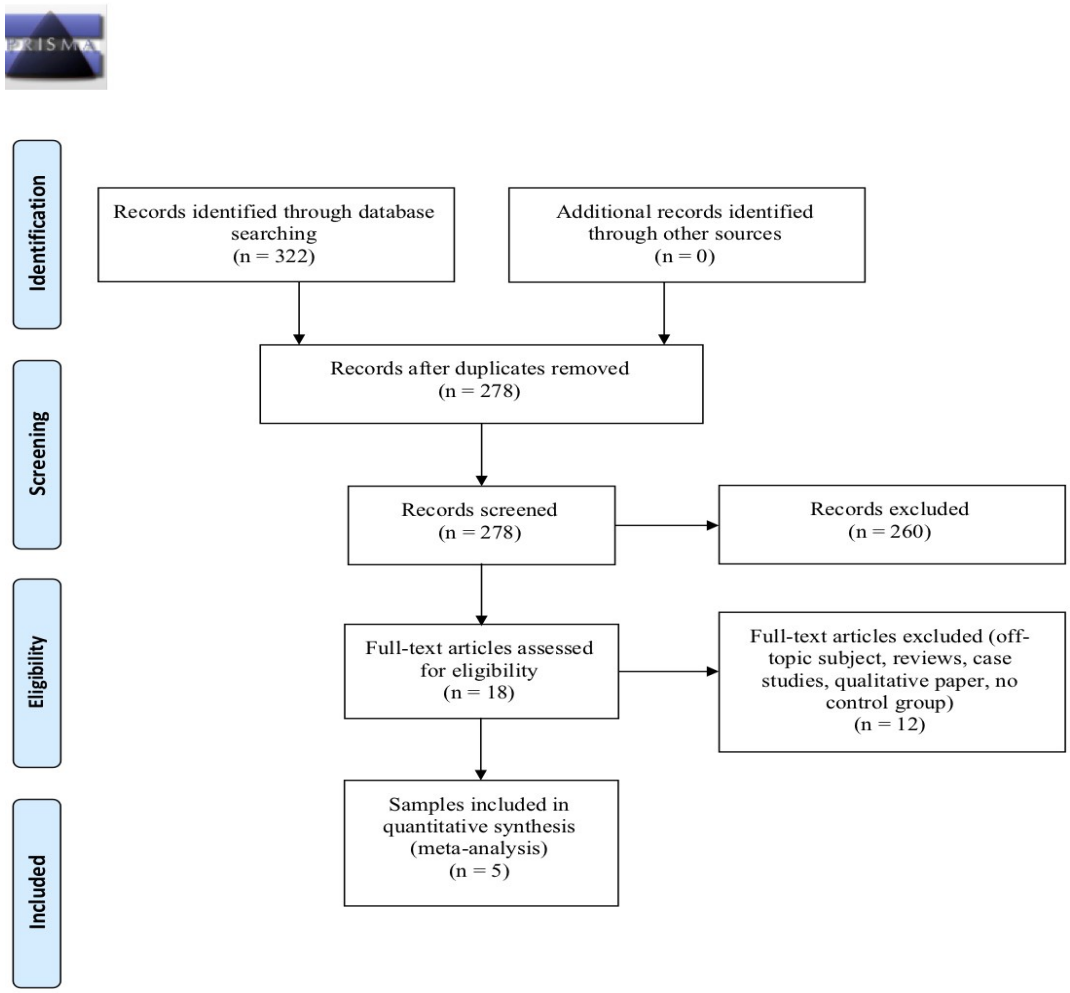
Search Strategy and Information Source

We searched for studies published up to July 2020. No studies were excluded from our meta-analysis because of their country of origin.

We searched for published studies in the following databases: PsychNet, PubMed, and Ebsco. The ProQuest Dissertations and Theses database was used to find unpublished theses. The following key- words were used in our search: “SCD”, “subjective cognitive decline”, “subjective cognitive impairment”, “subjective memory impairment”, “subjective memory decline”, “cognitive complaints”, “memory complaints”, “cognitive concerns”, “memory con- cerns”, “olfac*” and “smell”. After excluding duplicate studies, 322 titles and abstracts were reviewed (see Figure 1). Studies were excluded when they were off-topic (e.g., animal studies, assessment of other sensory modalities, absence of SCD group, etc.), reviews, case studies, qualitative papers or if they did not include a control group. This screening identified 18 potentially eligible studies.

Figure 1.

PRISMA Flowchart Illustrating the Selection of Studies



Note. Flowchart illustrating the selection of studies.

Study Selection

The first author (BJ) evaluated all of the selected studies to assess their eligibility according to the criteria mentioned above. He then sent the list of potentially eligible articles to a research assistant who was blind with respect to the purpose of this meta-analysis. An article was only included if it was approved by both evaluators based on the risk of bias assessment.

Risk of Bias in Individual Studies

Risk of bias for each of the selected studies was assessed independently by two evaluators [BJ and AR] according to the Newcastle-Ottawa Scale (NOS; Peterson et al., 2011). The NOS is a scale used to evaluate the quality of non-randomized case-control studies published in meta-analyses (i.e., evaluation of participants' selection, comparability between groups, ascertainment of olfactory identification), which was recommended by Zeng and colleagues in 2015 (Zeng et al., 2015). A consensus was reached after pooling the results (see Table 1). A score between 0 and 3 was considered a high risk of bias, between 4 and 6 a moderate risk of bias, and between 7 and 9 a low risk of bias. When disagreement emerged at this stage, it was agreed that the most conservative result would be selected. No major disagreement emerged and no studies were excluded following this evaluation.

Table 1.

Risk Bias Assessment of Included Studies

Authors (Year)	Participants' Selection	Comparability Between Groups	Ascertainment of Olfactory Identification	Risk Bias According to the NOS
Dhilla Albers et al. (2016)	+ Use of a neuropsychological battery and the Clinical Dementia Rating-Sum of Boxes by clinicians. + Controls were from the same community and without cognitive complaints. - No consecutive/random recruitment. - No description of controls' health history.	- No control for sex, age or other important factors.	+ Secure method to assess OI (OPID). + Same method for both groups.	Moderate
Risacher et al. (2017)	+ Use of the 20-item Cognitive Change Index, the Montreal Cognitive Assessment test and other tests assessing memory and executive functions. + Controls were from the same community and without cognitive complaints. - No consecutive/random recruitment. - No description of controls' health history.	+ Study control for age, sex and education.	+ Secure method to assess OI (UPSIT). + Same method for both groups.	Moderate
Soharabi et al. (2009)	+ Use of the Memory Functioning Questionnaire and the memory subtest of the Cambridge Mental Disorders of the Elderly Examination and the Mini-Mental State Examination. + Controls were from the same community and without cognitive complaints. - No consecutive/random recruitment. + Description of controls' health history.	- No control for sex, age or other important factors.	+ Secure method to assess OI (SSIT). + Same method for both groups.	Moderate

Table 1.

Risk Bias Assessment of Included Studies (continued)

Authors (Year)	Participants' Selection	Comparability Between Groups	Ascertainment of Olfactory Identification	Risk Bias According to the NOS
Tahmasebi et al. (2019)	+ Use of a complete neurological examination, a standard laboratory blood test, and psychometric testing including the Mini-Mental State Examination and the Neuropsychological Test Battery Vienna. Selections made by a professional consensus committee. + Controls were from the same community and without cognitive complaints. - No consecutive/random recruitment. + Description of controls' health history.	+ Study control for age and depression.	+ Secure method to assess OI (SSIT). + Same method for both groups.	Low
Weber (2003)	+ Use of the Mini-Mental State Examination and a clinical evaluation by a trained doctoral student in psychology. + Controls were from the same community and without cognitive complaints. - No consecutive/random recruitment. + Description of controls' health history.	+ Study control for education and depression.	+ Secure method to assess OI (CC-SIT). + Same method for both groups.	Low

Note. OI: olfactory identification. OPID: Odor Percept Identification. UPSIT: University of Pennsylvania Smell Identification Test. SSIT: Sniffin' Sticks Identification Test. CC-SIT: Cross-Cultural Smell Identification Test (CC-SIT). NOS: Newcastle-Ottawa Scale.

Analyses

Analyses were performed using Meta-Essential (Suurmond et al., 2017). For each study, Hedges' g was calculated to obtain a standardized effect size. When an article did not contain means and standard deviations, we calculated them when possible. When it was not possible, we contacted the authors to obtain the missing data. One author has been contacted and confirmed that two studies (Tahmasebi, Zehetmayer, Pusswald, et al., 2019; Tahmasebi, Zehetmayer, Stögmann, & Lehrner, 2019) used the same sample and provided us the data of the full sample. The combined effect size was then calculated. According to Brydges (2019), Cohen's guidelines (Cohen, 2013) probably overestimated average effect sizes in gerontology. After analyzing 88 meta-analyses in gerontology, he suggests that a $g = 0.16$ can be interpreted as a small effect size, $g = 0.38$ as a medium effect size and $g \geq 0.76$ as a large effect size. Finally, the more conservative random effects model has been used to compute the significance level of the mean effect sizes for each study since selected studies are not functionally 100% equivalent (i.e., not every study used the same olfactory identification test and the same exact design).

Risk of Bias Across Studies

To quantify heterogeneity in effect sizes, we used Cochrane's Q-statistic (Hedges & Olkin, 2014). We assumed heterogeneity if PQ was significant at $p < 0.05$. Then, the testing of potential moderators, such as age, sex and type of olfactory identification tests, was allowed if there was presence of heterogeneity. I^2 was generated to quantify the degree of heterogeneity among studies. Thus, the decision to test potential moderators or not was

not only based on a significance test, which could be underpowered with a small number of studies.

Publication bias was assessed using the visual inspection of the funnel plot and confirmed using Begg's rank test and Egger's regression test (Begg & Mazumdar, 1994; Egger et al., 1997).

Results

Study Selection and Characteristics

After analyzing full-text articles, six were eligible for extraction of quantitative data (see Figure 1). Two studies used the same sample, therefore the entire sample was used and counted for one study. Thus, five studies (samples) met the criteria for a total of 264 participants with SCD and 334 controls (see Table 2). According to study quality assessment, no studies were excluded for a high risk of bias (i.e.,< 3 on NOS scale) (see Table 1).

Table 2.

Characteristics of Studies Included in the Meta-Analysis

Authors (Year)	Olfactory Test	SCD Sample Size	Control Sample Size	SCD Mean Age (SD)	Control Mean Age (SD)	SCD Mean Score (SD)	Control Mean Score (SD)	Effect Size (Hedges' *g*)
Dhilla Albers et al. (2016)	OPID	74	70	77 (0.93)	75 (1.01)	0.67 (0.17)	0.69 (0.17)	-0.12
Risacher et al. (2017)	UPSIT	10	10	72.2 (6.4)	69.5 (6.9)	35.7 (3.3)	34.5 (2.3)	0.42
Soharabi et al. (2009)	SSIT	81	63	65.53 (7.3)	64.66 (7.73)	12.38 (2.18)	13.12 (1.49)	-0.39
Tahmasebi et al. (2019)	SSIT	69	161	66 (58.5/74)[a]	65 (57/73)[a]	12.16 (2.57)	12.83 (2.16)	-0.004
Weber (2003)	CC-SIT	30	30	65.9 (9.7)	66 (8.9)	9.7 (1.7)	10.3 (1.3)	-0.40

Note: OPID: Odor Percept Identification. UPSIT: University of Pennsylvania Smell Identification Test. SSIT: Sniffin' Sticks Identification Test. CC-SIT: Cross-Cultural Smell Identification Test (CC-SIT). Tahmasebi et al., 2019 data set was provided by the authors and as been used in both Tahmasebi et al., 2019 and Tahmasebi et al., 2019b articles.

[a] Median (25^{th} percentile/75^{th} percentile).

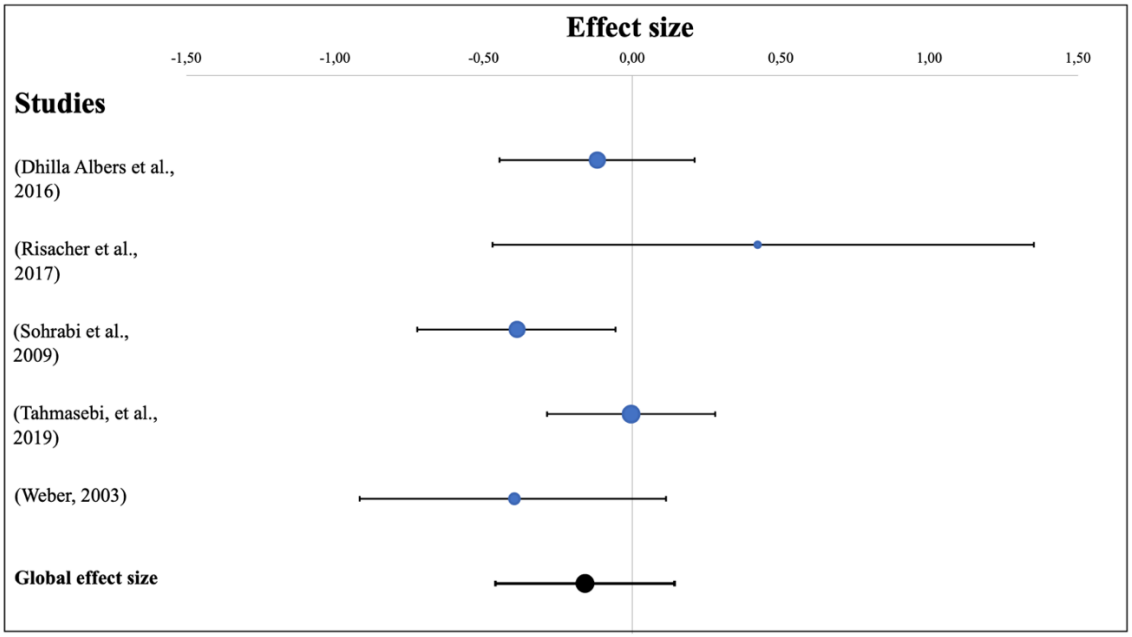
In all studies, the two compared groups were reported as equivalent in terms of age, and a significant difference on sex distribution was only found in one study (Risacher et al., 2017).

Main Effect

The aim of this meta-analysis is to determine whether identification olfactory ability is altered in SCD compared to healthy older adults. The analysis reveals a small effect size (g = -0.16, 95% CI [–0.46, 0.14]; k = 5) that was not significantly heterogenous (Q = 5.72, p_Q = 0.23) (see Figure 2). The homogeneity of the effect sizes was also confirmed with a second indicator (I^2 = 30.0%). Thus, moderator analysis was not necessary.

Figure 2.

Forest Plot of Effect Sizes



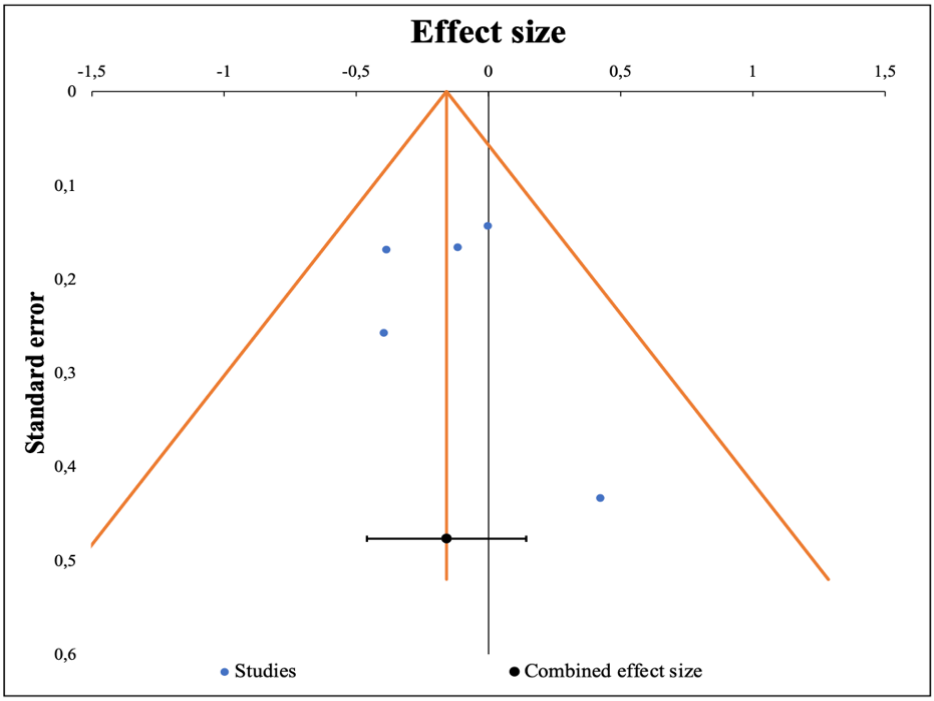
Note: Error bars represent 95% CIs.

Publication Bias

We did not performed regression-based analysis due to the insufficient number of included studies (5). Thus, a funnel plot was generated (see Figure 3). Asymmetry at the bottom (right) of the funnel plot may be due to a possible publication bias. This asymmetry suggests caution in interpretation of the results, until more studies have been conducted.

Figure 3.

Funnel Plot Random Effects (k = 5)



Note. Funnel plot for random-effects model (k = 5). The asymmetry in the distribution of studies may suggest potential publication bias or small-study effects.

Discussion

This study is the first meta-analysis on olfaction in individuals with SCD. We found that olfactory identification is slightly impaired in individuals with SCD compared to healthy older adults. In preclinical AD, at the SCD stage, individuals notice a decline in their cognition that causes them worries, but which classical neuropsychological tests are not able to detect (Jessen et al., 2014; Erk et al., 2011). Our results suggest that olfactory identification declines in individuals with SCD. It seems that olfactory identification tests

are more sensitive to objectify a decline than classical neuropsychological tests at the SCD stage.

Our results are in line with those from Sohrabi et al. (2009), who found that among olfactory functions, olfactory identification was linked to subjective memory complaints in community-dwelling older individuals, whereas olfactory detection, i.e., the ability to detect odors, was not. Other studies have shown that olfactory identification is associated with semantic memory and verbal capacities (Finkel et al., 2001; Schab, 1991). Thus, the decline of olfactory identification in individuals with SCD might be related to a decline in semantic memory and verbal capacities that is nevertheless not detectable with clinical tests. However, in 2019, Tahmasebi and colleagues did not find a significant link between olfactory identification and semantic memory in individuals with SCD (Tahmasebi, Zehetmayer, Pusswald, et al., 2019). They suggest that the decline in olfactory identification might be due to neuropathology consequences that are not limited to semantic memory and conclude that the ability to identify odors is distinct from semantic memory. This conclusion is in accordance with the model of aging and memory decline proposed by Larsson et al. (2016). This 3-component model includes olfactory, semantic and episodic memory and better explains the effect of age on memory performance in older adults than a 2-component model limited to semantic and episodic memory. In other words, they found that olfactory memory as indexed by episodic odor recognition and odor identification is modeled separately from episodic and semantic memory for visual and verbal information. Interestingly, they found that among older individuals, those

carrying APOE ε4 allele, which is a high-risk factor for developing AD, showed poorer memory performance, and these effects tended to be larger for olfactory memory. Thus, these results suggest that a decline in olfactory memory might be one of the early signs of AD. As a proxy of olfactory memory, assessing olfactory identification in individuals with SCD might help discriminate those who will convert to MCI or AD.

Another interesting point to discuss is the amplitude of the effect we found in our meta-analysis. No consensus had been reached on whether the olfactory decline found in MCI and dementia is already detectable in the SCD stage of the disease. Some studies found significant differences between healthy older participants and participants with SCD on olfactory identification scores (Sohrabi et al., 2009; Dhilla Albers et al., 2016), while other studies did not (Tahmasebi, Zehetmayer, Pusswald, et al., 2019; Tahmasebi, Zehetmayer, Stögmann, & Lehrner, 2019; Risacher et al., 2017; Weber, 2003). This meta-analysis confirmed that an olfactory decline is detectable at this early preclinical stage of the disease. The slight effect we found on olfactory identification may be due to the lack of specificity of the SCD diagnosis to discriminate those who will convert to MCI or AD from those who will remain stable. Interestingly, Jessen et al. (2014) propose a subcategory of SCD, the subjective cognitive decline plus or "SCD+" to better characterize those who are more at risk of developing an objective cognitive decline. SCD+ features include: (a) a subjective decline in memory, (b) an onset of SCD within the past 5 years, (c) and at 60 years and older, (d) a concern associated with SCD, (e) a persistence of SCD over time, (f) a seeking of medical help, and (g) a confirmation of

cognitive decline by an observer (Jessen et al., 2014; Jessen et al., 2020). Thus, one may hypothesize that individuals with SCD+ may have lower odor identification abilities than individuals with SCD or healthy older adults. Unfortunately, results from our meta-analysis cannot help verify this hypothesis given that the characteristics of the participants in the included studies were not sufficiently detailed to apply the SCD+ criteria.

Furthermore, in order to interpret our results on the pathological course of AD, we hypothesize that neuropathological changes occur on olfactory function at the earliest phase of the disease. In 2017, Risacher et al. showed that tau deposition, but not amyloid-β pathology, is associated with the olfactory identification score in individuals with SCD (Risacher et al., 2017). These data are consistent with the results of the literature where olfactory identification scores were related to neurofibrillar pathology in the entorhinal cortex and hippocampus (Wilson, Arnold, Schneider, Tang, & Bennett, 2007). Thus, the decline of olfactory function would be much closer to a marker of tau pathology. This is an interesting hypothesis given that tau predicts cognitive decline in individuals with SCD (Hessen et al., 2015; Sierra-Rio et al., 2016). Unfortunately, we cannot verify whether individuals with greater olfactory decline had a greater amount of tau pathology, since the tau pathology status of the participants was not available for all the included studies in our meta-analysis. Another AD biomarker is neurodegeneration. Structures involved in olfactory treatment, such as the hippocampus and the primary olfactory cortex, are atrophied in patients with AD and MCI. Notably, the atrophy of these structures is correlated with olfactory performance (Vasavada et al., 2017). The atrophy found in these

regions could also explain the olfactory decline observed at the SCD stage. Cross-sectional and longitudinal olfactory studies including AD pathologic and genetic markers (tau, amyloid-β, neurodegeneration and APOE ε4 positives) in combination with SCD+ components could allow for a better qualification of preclinical patients at risk of AD. In other words, future studies should focus on combining olfactory measurements with other AD markers in the SCD stage to better predict those at risk of AD.

This meta-analysis has some limitations. First, this study compared effect sizes that are from different behavioral olfactory identification tests. Some tests are well-known and commercially available, such as the Sniffin' Sticks (Hummel et al., 1997; Oleszkiewicz et al., 2019), the UPSIT (Doty et al., 1984), and the CC-SIT (Doty et al., 1996). The Sniffin' Sticks Identification test scores correlate with the UPSIT (Silveira-Moriyama et al., 2008), and the CC-SIT scores are similar and do not differ from those of the UPSIT (Doty et al., 1996). One study used the OPID test, which has shown similar results to the UPSIT in the classification of MCI of AD patients (Tabert et al., 2005). However, although these different tests measure the same construct and are comparable, they are not identical. Thus, the results of this meta-analysis should be interpreted with having this in mind. Second, this meta-analysis evaluated bias risks from each included study using the NOS. Considering the lack of gold standard tools to assess quality of case-control studies (e.g., SCD versus healthy older adults; Quigley et al., 2019; Ma et al., 2020), especially for non-randomized studies, we followed the recommendations of Zeng et al. (2015) and used the NOS to evaluate studies included in the meta-analysis, even though the NOS has not yet

been fully validated (Zeng et al., 2015; Quigley et al., 2019). Although the majority of the included studies demonstrated a low to moderate risk of bias, no studies were excluded based on this assessment. Results at the NOS scale revealed that the main shortcomings in terms of quality were found in the method used for participants' recruitment and the non-inclusion of variables such as age or sex in the analysis. Rigorous recruitment methods help avoid the risk of bias regarding the representativeness of the sampling. It is also important to include factors such as age or sex as covariates when analyzing olfactory scores since these variables are known to influence olfactory performance (Oleszkiewicz et al., 2019). A common strength of the selected studies was the assessment of olfactory identification by valid olfactory tests and the use of valid cognitive tests to qualify the lack of difference between SCD and control groups on the cognitive level. However, in most of the selected studies, confounding variables such as depression or anxiety symptoms were not accounted for in the analyses. Considering that these symptoms might lead the person to express an SCD, there is a need that future studies control for the influence of these variables (Jessen et al., 2014). Third, when analyzing publication bias, we were unable to perform regression-based analysis due to the small number of included studies. It highlights the dearth of studies on the sense of smell within individuals with SCD. Indeed, this meta-analysis included a low number of five different samples, which is the minimal number of studies required for random-effects models (Jackson & Turner, 2017). Thus, more studies with rigorous methodologies and larger samples of individuals with SCD are needed to conclude that olfactory identification is indeed a biomarker of AD at the SCD stage.

Following these limitations, we recommend that future studies include larger groups that are well-matched for sociodemographic characteristics. Furthermore, we recommend that a rigorous neuropsychological evaluation be conducted when selecting SCD participants. Future studies should also control for psychological variables that are susceptible to influence cognitive complaints such as anxiety or depression levels. Cognition should also be rigorously evaluated with more than a rapid screening test (i.e., the MMSE or the MoCA) when recruiting and differentiating healthy participants and SCD participants from MCI patients.

Conclusion

Olfactory identification is slightly impaired in individuals with SCD compared to healthy older adults. This first meta-analysis also highlights the limited literature on this topic and thus the need for more studies in order to better characterize individuals with SCD on olfactory capacities. To conclude, our results suggest that olfactory dysfunction may be a potential early marker of AD.

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Article scientifique 4

Olfaction and Declarative Memory in Aging: A Meta-Analysis

Article scientifique 4
Olfaction and Declarative Memory in Aging: A Meta-Analysis[5]

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Abstract

Olfactory and declarative memory performances are associated, as both functions are processed by overlapping medial-temporal and prefrontal structures and decline in older adults. While a decline in olfactory identification may be related to a decline in declarative memory, the relationship between olfactory detection threshold and declarative memory remains unclear. In this meta-analysis, we assessed (1) the relationship between olfactory identification/detection threshold and verbal declarative memory in cognitively normal older adults, and (2) the effect of age on these relationships. We included articles from PsychNet, PubMed, and Academic Search Complete according to the following criteria: (1) inclusion of cognitively normal older adults, (2) assessment of episodic or semantic memory, and (3) assessment of olfactory identification or detection threshold. Seventeen studies and 22 effect sizes were eligible and included in this meta-analysis. Olfactory identification was associated with episodic (small effect size: $r = .19$; $k = 22$) and semantic memory (small effect size: $r = .16$; $k = 23$). Similarly, the olfactory detection threshold was associated with both episodic (small to medium effect size: $r = .25$; $k = 5$) and semantic memory (small effect size: $r = .17$; $k = 7$). Age was found to moderate the relationship between olfactory detection threshold and memory performance. Both olfactory identification and detection threshold performances are associated with declarative memory in older adults, and age only moderates the relationship between olfactory detection threshold and declarative memory performances.

Keywords: Olfaction, Episodic Memory, Semantic Memory, Aging, Meta-Analysis.

Introduction

Olfactory function and declarative memory are associated in young and older adults (e.g. Hedner et al., 2010; Knight et al., 2020; Larsson et al., 2016; Lehrner, 1999). Compared to procedural memory, declarative memory is a long-term memory involving explicit, conscious storage, and retrieval of factual information or previous experiences (Ullman, 2004). Declarative memory encompasses episodic and semantic memory, which are two distinguishable concepts: episodic memory pertains to the memory of personally experienced events that occurred at specific times and places, while semantic memory refers to facts, concepts, and general knowledge (Tulving, 1972).

Olfaction is the sense by which odors are perceived. Most commonly, olfaction is assessed through odor identification and odor detection threshold tasks. Olfactory identification tasks measure the ability to identify or associate a target odor among different labels, while olfactory detection threshold tasks measure the lowest concentration of an odorant that can be detected reliably. Olfactory identification is often characterized as a "central" olfactory function because of its relation to higher cognitive functions such as executive function, and episodic and semantic memory (Dulay et al., 2008; Economou, 2003; Larsson, 2004). More specifically, some authors have conceptualized olfactory identification as a function involving semantic memory for olfactory stimuli, since odor identification relies on an individual's prior specific knowledge to properly label the target odor (Hedner et al., 2010; Larsson, 1997; Larsson et al., 2016; Schab, 1991).

Key structures supporting learning and retrieval of previously learned information (Gabrieli et al., 1997; Squire, 2004; Squire & Zola, 1991, 1996) are also involved in the identification of olfactory stimuli (i.e., the hippocampus, the entorhinal and the parahippocampal cortex). On a structural level, the entorhinal cortex is part of the primary olfactory cortex, as it receives direct input from the olfactory bulb (Gottfried, 2010; Lundström et al., 2011), and the hippocampus receives olfactory information from entorhinal projections; only three synapses separate it from the peripheral receptive structures in the olfactory mucosa (Schwerdtfeger et al., 1990; Staubli et al., 1984, 1986). On a functional level, the hippocampus, parahippocampal and entorhinal cortex are activated during both olfactory stimulation (Steffener et al., 2021; Torske et al., 2021) and olfactory identification tasks (Kjelvik et al., 2012, 2021; Kose et al., 2021).

Olfactory detection threshold, in turn, has been suggested to reflect the functioning of the peripheral olfactory system (Hedner et al., 2010; Hummel et al., 2007; Moberg, 1999) since several pathologies affecting the peripheral olfactory system lead to a decreased sensitivity for olfactory stimuli (Landis et al., 2005; Nordin & Brämerson, 2008; Patel et al., 2022). For instance, septal deviation (Pfaar et al., 2004) and allergic rhinitis (Stuck et al., 2003) are associated with a decreased sensitivity for olfactory stimuli without any alteration in the ability to identify these stimuli.

However, olfactory detection threshold and identification functions may not completely be independent, as olfactory detection threshold and identification

performances are associated (Doty et al., 1984, 1994). This suggests that olfactory detection threshold function may involve some cognitive processes. This hypothesis is further supported by the common decline in olfactory detection threshold and memory in older adults (Dulay & Murphy, 2002; Dulay et al., 2008). Key structures to support this hypothesis are the hippocampal and prefrontal regions, as they are both vulnerable to the aging process (Bartsch & Wulff, 2015; Bettio et al., 2017), related to odor detection (Igarashi et al., 2014; Murphy et al., 2003; Potter & Butters, 1980; Steffener et al., 2021; Zhang et al., 2019), and memory functioning (Borders et al., 2022; Cabeza et al., 2002; Kesner & Hunsaker, 2010; Melrose et al., 2020; Sexton et al., 2010).

The association between olfaction and memory is of particular interest in older adults since this population is at risk of developing olfactory and memory decline. A study involving more than 9000 participants showed that performance in both olfactory identification and detection threshold decline in adulthood and more severely from the age of 60 onwards (Oleszkiewicz et al., 2019). In healthy adults above 60 years of age, roughly 40% show olfactory impairment while a similar proportion exhibits some sort of memory decline (Dintica et al., 2019; Oleszkiewicz et al., 2019; Small, 2001). Even semantic memory, which is relatively preserved in aging, plateaus at around 60 years of age (Salthouse, 2019).

A decline in both olfactory and memory performances is also found in Alzheimer's disease. Indeed, decline in both declarative memory and olfactory function are among the first symptoms to appear in the progression of Alzheimer's disease, possibly as a result of

tau pathology accumulation, which first appears in the trans-entorhinal and hippocampal regions of the brain (Aschenbrenner et al., 2018; Braak & Braak, 1991; Hessen et al., 2015; Risacher et al., 2017; Weigand et al., 2021). In this context, it is noteworthy that olfactory impairment in Alzheimer's disease and in mild cognitive impairment is more pronounced for olfactory identification than for olfactory detection threshold (Rahayel et al., 2012; Roalf et al., 2017). Since memory impairment occurs early in the development of Alzheimer's disease, it has been hypothesized that impairment of higher cognitive processes may explain functional differences between olfactory identification and olfactory detection threshold (Rahayel et al., 2012). As a consequence, olfactory identification, as opposed to the olfactory detection threshold, is considered to be an early clinical marker of Alzheimer's disease (Jobin et al., 2021; Quarmley et al., 2016; Roalf et al., 2017).

In the same vein, the decline in olfactory identification has been associated with a decline in declarative memory in cognitively normal older adults. More specifically, impaired olfactory identification, which was found to predict a general cognitive decline in healthy older adults (Olofsson et al., 2009; Sohrabi et al., 2012), appears to affect verbal episodic and semantic memory (Dintica et al., 2019; Swan & Carmelli, 2002). Similarly, older adults genotyped as apolipoprotein E-ε4 (APOE-ε4) carriers – a risk factor for Alzheimer's disease – were found to experience a decline in episodic memory over one to two decades, which was also associated with an impairment to identify olfactory stimuli (Olofsson et al., 2016). On the other hand, the age-related decline in olfactory detection

threshold performance has been explained by anatomical and physiological changes to peripheral structures (such as nasal diseases, damages to the olfactory epithelium, ossification of the cribriform plate, and neurochemical changes) and central nervous structures (e.g., damage to olfactory cells receptor, and neuronal damages associated with neurodegenerative disease pathologies) (for reviews, see Doty & Kamath, 2014; Olofsson et al., 2021), rather than changes in cognition or memory.

According to the literature, the aging-associated decline in olfactory identification is associated with a decline in declarative memory, while the relationship between olfactory detection threshold and declarative memory remains unclear. Because the relationship between olfactory function and memory performance has not yet been evaluated systematically in older adults, this meta-analysis aimed to provide a comprehensive overview of (1) the relationship between olfactory identification/detection threshold and verbal declarative memory in cognitively normal older adults, and on (2) the potential effect of age on these relationships.

Methods

Eligibility criteria of the studies selected. To be eligible, studies had to examine the relation between (1) a memory score ((a) episodic or (b) semantic) and (2) an olfactory score ((a) identification or (b) detection threshold). Participants of selected studies had to be cognitively normal and aged > 45 years, the mean age of participants had to be > 55 years. This criterion is based on previous studies showing that both memory and

olfaction already started declining before the age of 55 (Oleszkiewicz et al., 2019; Salthouse, 2009, 2019). Studies involving participants with any condition that could affect cognition (i.e., psychiatric diagnoses and/or neurological conditions) or olfaction were excluded.

Outcome

Included studies had to measure verbal declarative memory. (a) Episodic memory measurements included (i) immediate and (ii) delayed recalls of word lists, as measured by the California Verbal Learning Test (CVLT, Delis et al., 2008), the Rey Auditory Verbal Learning Test (RAVLT, Schmidt, 1996) or the Hopkins Verbal Learning Test (HVLT, Benedict et al., 1998). Next, (b) semantic memory had to be measured by (i) categorical fluency tasks, as measured by the Delis-Kaplan Executive Function System Battery Tests (Delis et al., 2001), (ii) denomination, (iii) general knowledge, and (iv) vocabulary tasks, as evaluated through subtests from the Wechsler Adult Intelligence Scale (Wechsler, 2008). We did not include correlations from composite scores that included other olfactory or memory components.

Typically, (a) olfactory identification was evaluated by a validated behavioral test, e.g., the Sniffin'Sticks Identification Test (Hummel et al., 1997), the University of Pennsylvania Smell Identification Test (UPSIT, Doty et al., 1984), or any other common olfactory identification test. In short, olfactory identification tasks involve matching an odor to the right label among different choices. (b) Olfactory detection threshold was

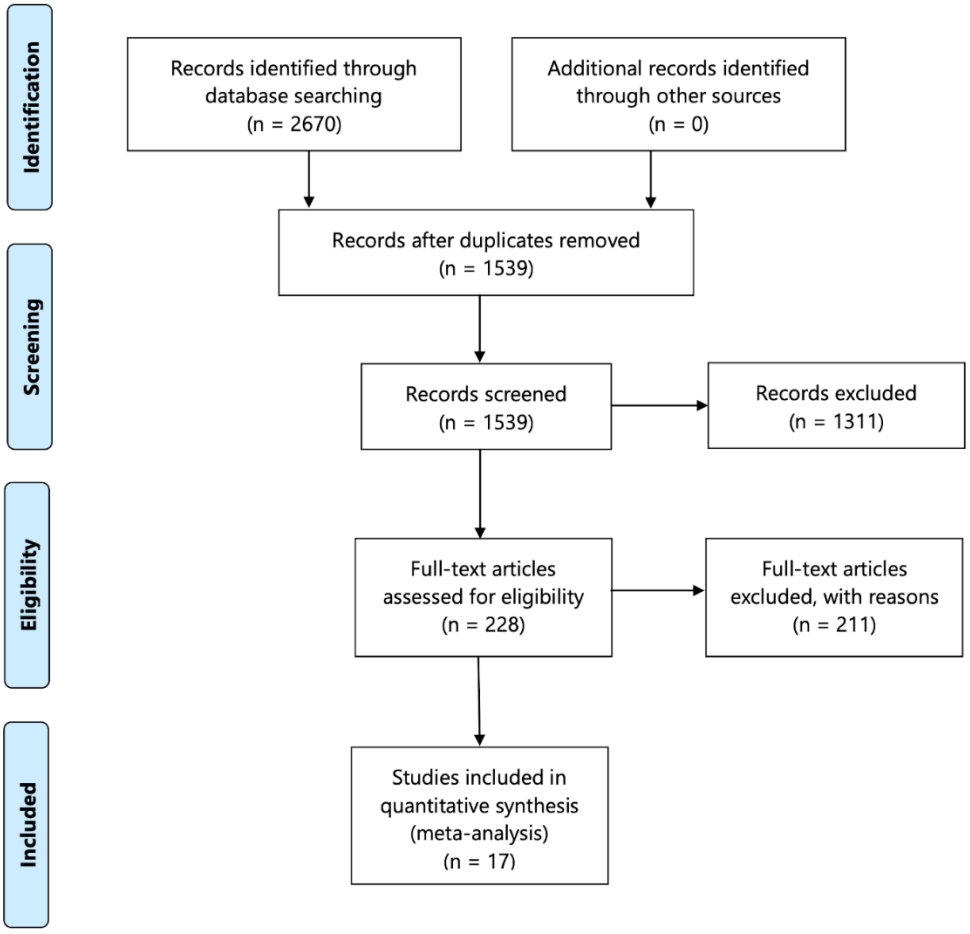
assessed using the Sniffin'Sticks Threshold Test (Hummel et al., 1997) or another equivalent test. Typically, threshold test procedures require the participant to choose between three stimuli that are presented sequentially. Among these stimuli, only one is odorous (target). The concentration of the target changes between trials (for a more detailed procedure description see (Rumeau et al., 2016).

Search Strategy and Information Source

We searched for studies published up to January 1st, 2023. No studies were excluded from our meta-analysis based on their country of origin and only studies published in English were included. We searched for published studies in the following databases: PsychNet, PubMed, and Academic Search Complete (Ebsco). The following keywords were used in our search ("olfac*" OR "smell" OR "odor") AND ("memor*" OR "cogniti*") AND ("correlat*"). We also verified the presence of potentially eligible studies in the references of eligible studies found in database extraction. After excluding duplicate studies, 1539 titles and abstracts were reviewed. Studies were excluded when they were off-topic (e.g., animal studies, assessment of other sensory modalities, etc.), or when they qualified as reviews, case studies, qualitative papers, or if they only included clinical groups. Only direct correlations between a specific cognitive domain and a specific olfactory domain were eligible. Two hundred and twenty-eight studies were identified for a full-text examination (see Figure 1).

Figure 1

. PRISMA Flowchart Illustrating the Selection of the Studies



Note. Flowchart illustrating the selection of the studies included in this meta-analysis.

Study Selection

The eligibility of the studies was assessed by BJ and FRC according to the criteria mentioned above. Articles were included if they were approved by both BJ and FRC based on the risk of bias assessment (Munn et al., 2020).

Risk of Bias in Individual Studies

The risk of bias was evaluated for each selected study according to the Joanna Briggs Institute's Checklist for Analytical Cross-Sectional Studies as recommended (Ma et al., 2020; Munn et al., 2020), addressing the possibility of bias in design, conduct and analysis. BJ and FRC evaluated each eligible study according to the inclusion criteria mentioned above. When disagreement emerged at this stage, the most conservative result was selected. A consensus was reached after pooling the results and no major disagreement emerged. No studies were excluded following this evaluation.

Analyses

We performed analyses using Meta-Essentials (Suurmond et al., 2017). We used Fisher's r-to-z transformation for each correlation coefficient to determine an effect size for each sample. Next, we calculated combined effect sizes. According to Cohen's guidelines, we interpreted $r = .10$, $r = .30$, and $r = .50$ as small, medium, and large effect sizes, respectively (Cohen, 2013). We used the more conservative random effects model to compute the significance level of the mean effect sizes.

Risk of Bias Across Studies

We qualified heterogeneity using Cochrane's Q-statistic and quantified the degree of heterogeneity using I2 among effect sizes (Hedges & Olkin, 2014). We assumed heterogeneity if PQ was significant at $p < 0.05$. When heterogeneity was assumed and the number of included studies per subgroup was sufficient as suggested (Fu et al., 2011;

Higgins et al., 2019), we then tested the moderating effect of each measure of episodic memory (i.e. (i) immediate and (ii) delayed recalls of word lists) and semantic memory (i.e. (i) categorial fluency, (ii) denomination, (iii) general knowledge, and (iv) vocabulary).

Finally, we performed meta-regressions with age as a potential moderator for the relationships between olfactory identification and olfactory detection threshold and declarative memory performances.

We qualified publication bias using both visual inspection of funnel plots and Rosenthal's failsafe-N test that gives the number of potential unpublished studies that are required to turn the combined effect size statistically insignificant or to change the conclusions of the meta-analysis (Rosenthal, 1979).

Results

Correlations Between Olfactory Identification and Declarative Memory

After analyzing full-text articles, twenty-two correlations between olfactory identification and episodic memory scores, and twenty-three correlations between olfactory identification and semantic memory scores, were included in the meta-analysis (see Table 1). We present effect size correlations between olfactory identification and episodic and semantic memory in Figure 2. The analysis on olfactory identification and episodic memory scores revealed a significant small effect size (r = .19, 95% CI [.13,

.25]; k = 22) that was significantly heterogeneous (Q = 50.69, $p_Q < 0.001$; $I^2 = 58.58\%$). We further found significant small effect size correlations between olfactory identification scores and (i) immediate recall (r = .18, 95% CI [.10, .27]; k = 15) and (ii) delayed recall scores (r = .20, 95% CI [.09, .31]; k = 7).

Table 1.

Olfactory Identification and Memory Correlations

Study	Participants Characterization	*n*	Mean Age (SD)	Olfactory Test	Memory Test	Effect Size
(Bailie, 2009)	Aged 55 and over, from skilled nursing homes, independent living facilities, and senior citizen support groups.	45	75.76 (10.30)	Multiple Intensity Odor Identification Test	CVLT BNT CF	.40 .25 .67
(Chen et al., 2018b)	Evaluated by two psychiatrists, including a comprehensive neuropsychological assessment.	154	67.63 (8.5)	Sniffin' Sticks	AVLT LMT CF	.22 .10 .09
(Cozac et al., 2017)	Participants screened by neuropsychologist and neurologist.	21	67.5 (N/A)	Sniffin' Sticks	SVCF	-.08
(Devanand et al., 2019)	Intact cognition after a neuropsychological assessement.	92	77.55 (4.49)	UPSIT	SRT	Total Immediate Recall = .27 Delayed Recall = .16
(Dulay et al., 2005)	– Older adults from living retirement communities. – Exclusion of participants with known neurologic or psychiatric conditions. – DRS-2 > 131	80	77.08 (8.50) (Full-Sample)	UPSIT	CVLT-II Short-Form	.01
(Hedner et al., 2010)	All participants were in good health and underwent a detailed ear-nose-throat (ENT) examination.	170	57.2 (13.8)	Sniffin' Sticks	16 Concrete Nouns Test	.21
(Larsson, 2004)	Population based study. MMSE score > 24 and absence of subjective olfactory disorder.	1906	67.5 (N/A)	SOIT	CF Vocabulary	.15 .31

Table 1.

Olfactory Identification and Memory Correlations (continued)

Study	Participants Characterization	*n*	Mean Age (SD)	Olfactory Test	Memory Test	Effect Size
(Larsson et al., 2016)	Population based study including geriatric, neurological, and psychiatric assessments; and neuropsychological testing.	2280	71.46 (9.68)	Sniffin' Sticks	16 Unrelated Nouns Test	Free Odor Identification = .26 Total Odor Identification = .25
					Vocabulary	Free Odor Identification = .19 Total Odor Identification = .21
					GK	Free Odor Identification = .09 Total Odor Identification = .07
					Vocabulary	Free Odor Identification = .19 Total Odor Identification = .21
(Liu et al., 2022)	Evaluation made by at least two neurologists with expertise in dementia, a neuropsychologist, and a geriatric psychiatrist.	189	67.29 (7.49)	Sniffin' Sticks	AVLT (RAVLT)	Short-term delayed recall = .30 Long-term delayed recall = .20
					BNT	0.16
					Verbal Fluency Test	0.13
(Makowska et al., 2011)	MMSE > 27.	30	72.33 (6.29)	PST	ADAS-COG Cognitive Subscale – Word Recall	Absolute Identification = -.43 Forced Choice = -.40
(Seubert et al., 2020)	MMSE > 24.	422	69.73 (8.76)	Sniffin' Sticks	30-Item Vocabulary Test Free Recall	.14
					30-Item Vocabulary Test Synonyms	.21

Table 1.

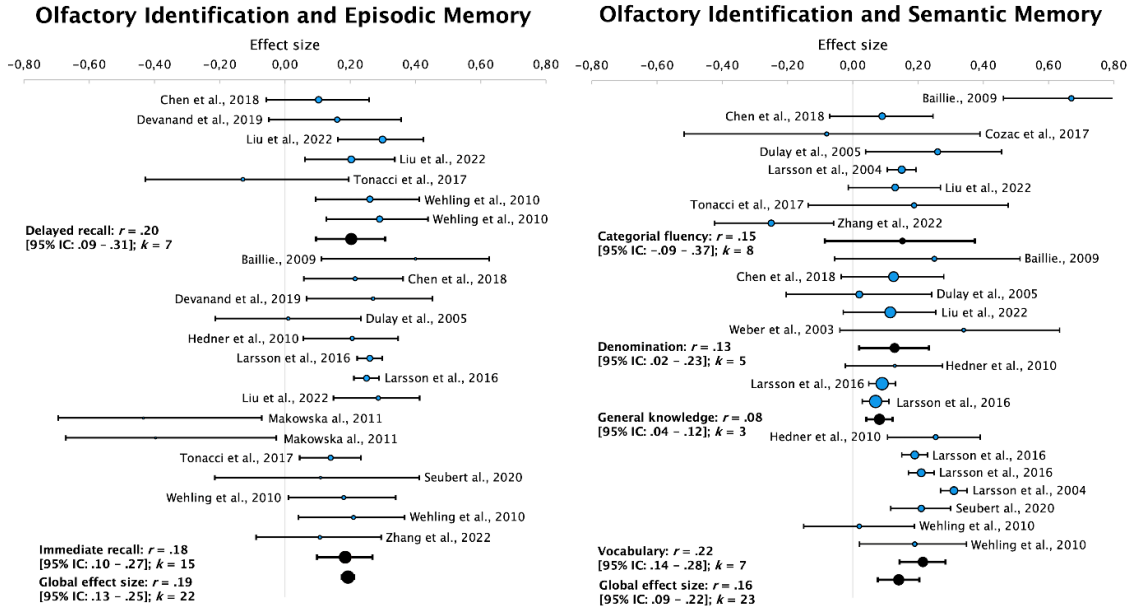
Olfactory Identification and Memory Correlations (continued)

Study	Participants Characterization	*n*	Mean Age (SD)	Olfactory Test	Memory Test	Effect Size
(Wehling et al., 2010)	No neurological or psychiatric disorders, head trauma, or other significant medical conditions. Normosmia assessed by an olfactory detection test.	136	61.7 (7.8)	SOIT	CVLT	Cued Odor Identification: Total Learning = .18 Long Delay Free Recall = .26 Free Odor Identification: Total Learning = .26 Long Delay Free Recall = .29
					Vocabulary (WASI)	Cued Odor Identification = .02 Free Odor Identification = .19
(Zhang et al., 2022)	Assessed by two neuropsychiatrists, one neuropsychologist, and one psychiatrist.	105	67.30 (6.5)	Sniffin' Sticks	AVLT (RAVLT) Animal Verbal Fluency Test	.11 -.25

Note. BNT: Boston Naming Test; CC-SIT: Cross-Cultural Smell Identification Test; CF: Category Fluency; GKQ: General Knowledge; LMT: Logical Memory Test; MMSE: Mini-Mental State Evaluation; N/A: Not available; PST: Pocket Smell Test; RAVLT: Rey Auditory Verbal Learning Test; SOIT: Scandinavian Odor Identification Test; SRT: Selective Reminding Test; SVCF: Semantic Verbal Categorial Fluency; UPSIT: University of Pennsylvania Smell Identification Test; WASI: Wechsler Abbreviated Scale of Intelligence.

Figure 2.

Forest Plot of Effect Sizes for the Correlations Between Olfactory Identification and Declarative Memory



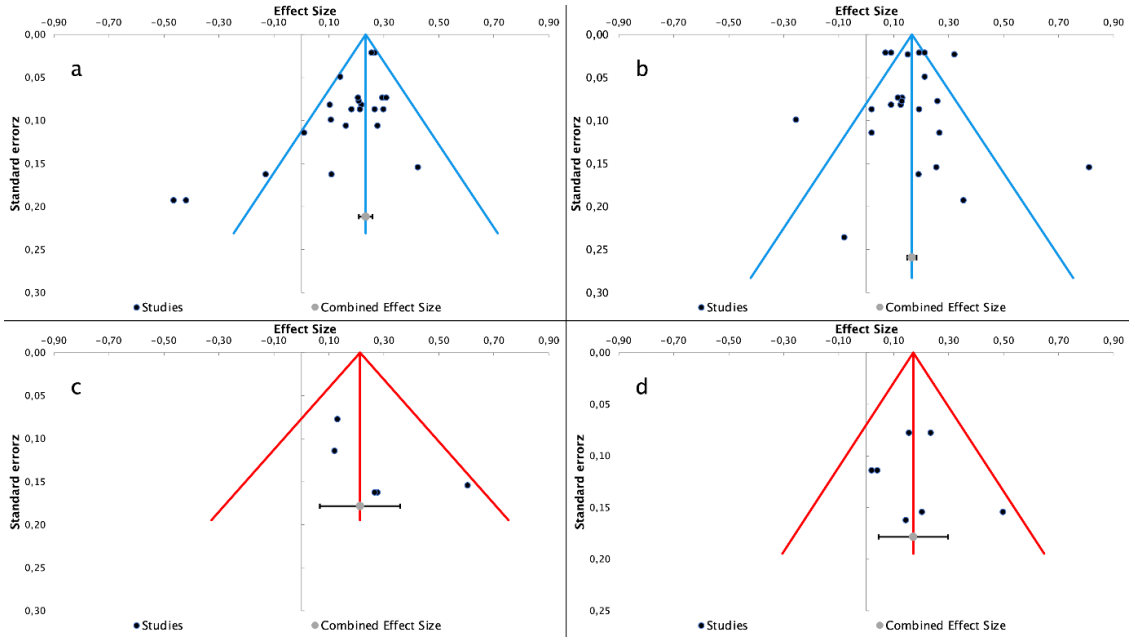
Note. Forest plot of effect sizes for the correlations between olfactory identification and episodic memory (left) and semantic memory (right). Error bars represent 95% Cis.

The correlational analysis on olfactory identification and semantic memory scores revealed a significant small effect size (r = .16, 95% CI [0.09, 0.22]; k = 23) that was significantly heterogeneous (Q = 134.27, $p_Q < 0.001$; I^2 = 83.61). We found significant correlations for (ii) denomination tests (r = .13, 95% CI [.02, 0.23]; k = 5; small effect size), (iii) general knowledge tests (r = .08, 95% CI [.04, .12]; k = 3; small effect size), and (iv) vocabulary (r = .22, 95% CI [0.14, 0.28]; k = 7), but not for i) categorical fluency tests (r = .15, 95% CI [-.09, .37]; k = 8).

Rosenthal's failsafe-N was 1302 for the correlation between olfactory identification and episodic memory, and 2054 for the correlation between olfactory identification and semantic memory, indicating no publication bias. Asymmetry at the bottom (left) of the funnel plot (see Figure 3), which analyzes the relationship between olfactory identification and episodic memory, suggests an overrepresentation of a negative relationship between these two concepts and, therefore, a possible publication bias.

Figure 3.

Funnel Plots of Each Meta-Analysis



Note. Funnel plot of standard errors z of effect sizes for each meta-analysis. a) represents the funnel plot of the relationship between olfactory identification and episodic memory; b) olfactory identification and semantic memory; c) olfactory detection threshold and episodic memory; d) olfactory detection threshold and semantic memory. Error bars represent 95% CIs.

Correlations Between Olfactory Detection Threshold and Declarative Memory

After analyzing full-text articles, five correlations between olfactory detection threshold and episodic memory scores and seven correlations between olfactory detection threshold and semantic memory scores were included in the meta-analysis (see Table 2). Figure 4 shows effect size correlations between olfactory detection threshold and episodic memory (left) and semantic memory (right). The analysis of olfactory detection threshold and episodic memory scores revealed a significant small-to-medium effect size (r = .25, 95% CI [.02, .45]; k = 5) that was homogenous (Q = 8.48, p_Q = 0.08; I^2 = 52.81).

Table 2.

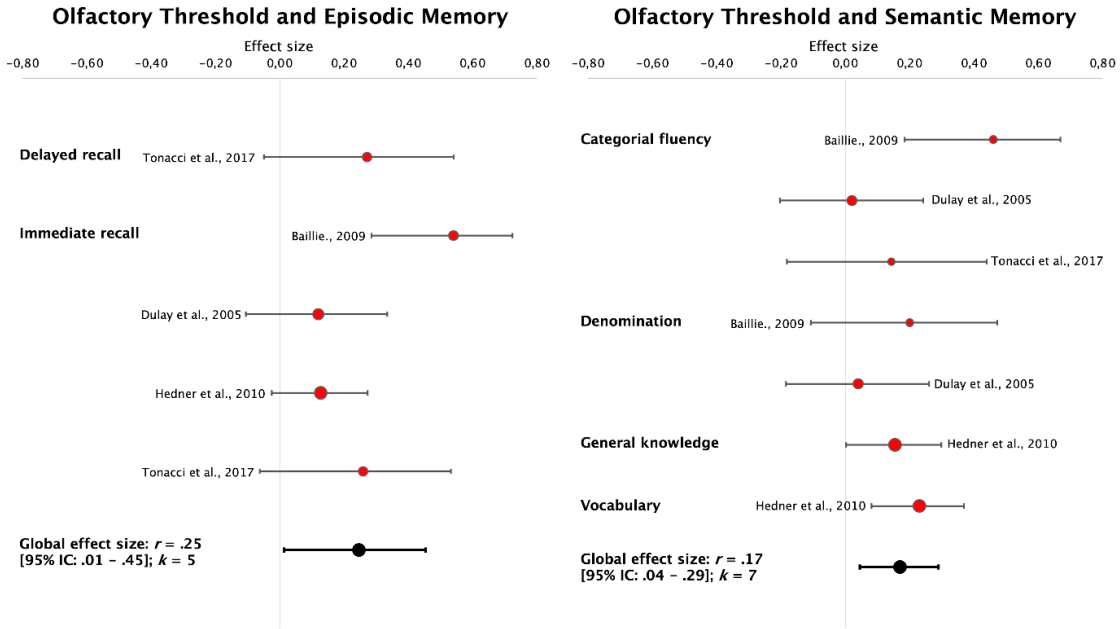
Olfactory Detection Threshold and Memory Correlations

Study	Participants Characterization	*n*	Mean Age (SD)	Olfactory Test	Memory Test	Effect Size
(Bailie, 2009)	Aged 55 and over, from skilled nursing homes, independent living facilities, and senior citizen support groups.	45	75.76 (10.30)	Four Odor Threshold Tests for *N*-Butanol (3-AFC)	CVLT BNT CF	.54 .20 .46
(Dulay et al., 2005)	– Older adults from living retirement communities. – Exclusion of participants with known neurologic or psychiatric conditions. – DRS-2 > 131	80	77.08 (8.50) (Full-Sample)	PEAT (2-AFC)	CVLT-II Short-Form BNT Short-Form CF	.12 04 .02
(Hedner et al., 2010)	All participants were in good health and underwent a detailed ear-nose-throat (ENT) examination.	170	57.2 (13.8)	Sniffin' Sticks (3-AFC)	16 Concrete Nouns Test GK Vocabulary	.13 .15 .23
(Tonacci et al., 2017)	Neuropsychological assessment was performed	41	73.5 (4.3)	Sniffin' Sticks (3-AFC)	RAVLT GK	Immediate Recall = .26 Delayed Recall = .27 .14

Note. AFC: Alternative Forced Choice; BNT: Boston Naming Test; CF: Category Fluency; CVLT: California Verbal Learning Test; DRS-2: Dementia Rating Scale 2; GK: General Knowledge; PEAT: Two Alternative Forced-choice Phenyl Ethyl Alcohol Threshold; RAVLT: Rey Auditory Verbal Learning Test.

Figure 4.

Forest Plot of Effect Sizes for the Correlations Between Olfactory Threshold and Declarative Memory



Note. Forest plot of effect sizes for the correlations between olfactory threshold and episodic memory (left) and semantic memory (right). Error bars represent 95% CIs.

Next, the analysis of olfactory detection threshold and semantic memory scores revealed a significant small effect size (r = .17, 95% CI [.04, .29]; k = 7) that was homogenous (Q = 8.33, p_Q = 0.26; I^2 = 27.94). While most of the studies included a three-alternative forced-choice procedure to assess olfactory detection threshold, the one study (Dulay et al., 2005) that included a two-alternative forced-choice procedure showed a smaller effect size compared to the others (see Table 2).

Rosenthal's failsafe-N was 33 for the correlation between olfactory detection threshold and episodic memory, and 25 for the correlation between olfactory detection

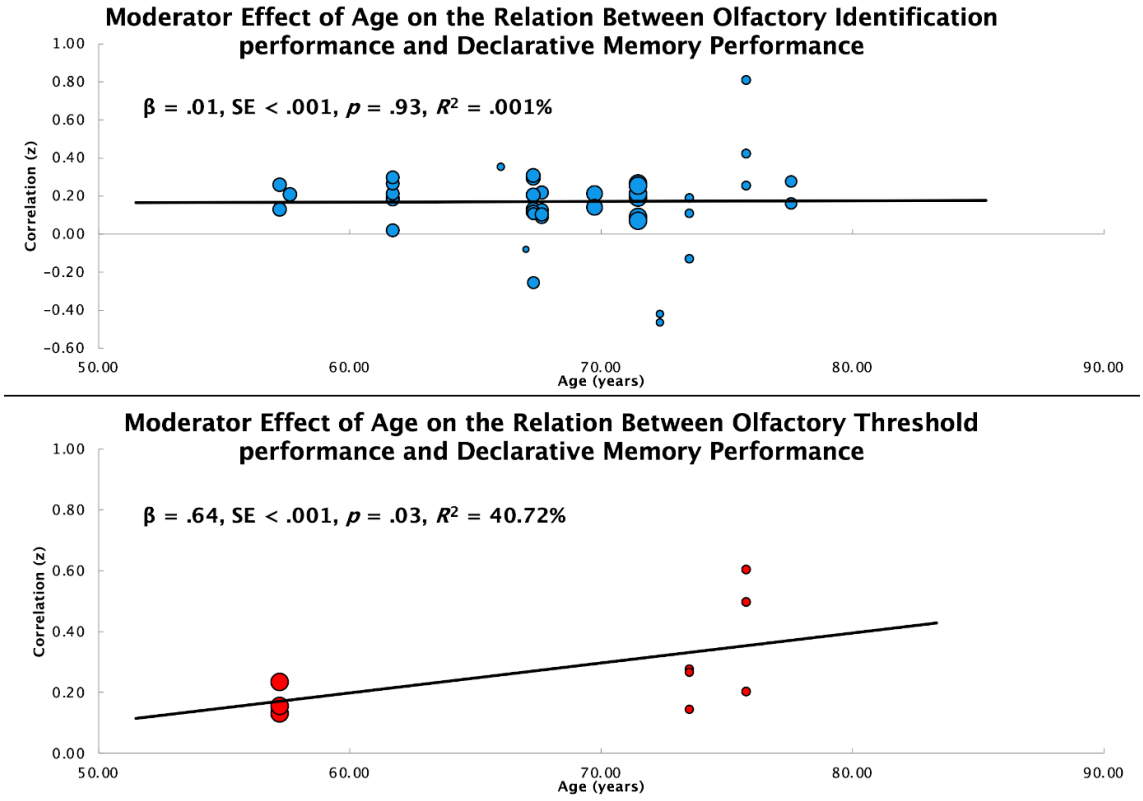
threshold and semantic memory, indicating a potential publication bias. However, the generated funnel plot showed no major asymmetry, indicating no potential publication bias (see Figure 3).

Age as a Moderator

Meta-regressions showed that age was not a significant moderator of the relationship between olfactory identification and declarative memory performance in older adults. However, we found a significant moderator effect of age on the relationship between olfactory detection threshold and declarative memory performance, showing a higher relationship between olfactory detection threshold and memory scores in studies including participants with an older mean age (see Figure 5).

Figure 5.

Moderator Effect of Age



Note. Meta-regressions evaluating the moderator effect of age on the relationship between olfactory capacities and declarative memory. The analyses were completed with studies whose information was available (two studies were missing).

Discussion

In this meta-analysis, we aimed to assess the relationship between olfactory and verbal declarative memory performance in a cognitively normal older adult population. We found that (1) olfactory identification and detection threshold are both significantly correlated with declarative memory in cognitively normal older adults, with comparable

effect sizes, and (2) age moderates the relationship between olfactory detection threshold and declarative memory performances.

As expected, our meta-analytical results are in line with previous reports suggesting that olfactory identification and episodic memory are associated in older adults (Larsson et al., 2016; Chen et al., 2018; Devanand et al., 2019; Seubert et al., 2020) and younger adults (Hedner et al., 2010). Patients suffering from diseases associated with episodic memory deficits, such as Alzheimer's disease, also typically exhibit olfactory identification dysfunction (Bahar-Fuchs et al., 2010; Park et al., 2018; Rahayel et al., 2012). Olfactory identification is the first observed olfactory deficit in Alzheimer's disease (Hedner et al., 2010; Murphy et al., 2003; Serby et al., 1991), and a lower olfactory identification score is associated with episodic memory decline in patients with Alzheimer's disease (Knight et al., 2020).

Our results also support the notion of an association between olfactory identification and semantic memory. This link is not surprising as olfactory identification requires labelling a specific odor, which relies on one's semantic knowledge (Larsson, 1997; Schab, 1991). However, the association is characterized by a small effect size. This result might support a model of an olfactory memory as being separate from – although influenced by – verbal declarative memory (Larsson et al., 2016), an idea initially suggested by Herz and Engen (1996). Larsson et al. (2016) suggested various hypotheses to explain the differences between olfactory memory and memory for other sensory

stimuli, such as differences with respect to the neuroanatomical organization of olfactory imagery capacity (Arshamian & Larsson, 2014) and the olfactory-language network (Olofsson et al., 2014). Indeed, connections between the piriform cortex and the cortical regions associated with semantic networks are more direct although less elaborate, compared to other sensory modalities. This difference could lead to a lack of olfactory feature analysis, a poor translation of odor objects to lexical representations, and a cumulative deterioration of signal quality over different processing stages from odor input to odor identification (Herz, 2005; Olofsson et al., 2013, 2014; Olofsson & Gottfried, 2015).

Next, our results showed a significant association between olfactory detection threshold and declarative memory scores with a small effect size, suggesting that olfactory detection threshold procedures involve mnesic processes (Dulay et al., 2008). Two possible hypotheses can be put forward to explain these results. One hypothesis (1) relies on the procedure for assessing olfactory detection threshold. Typically (e.g. Sniffin' Sticks olfactory threshold test, Hummel et al., 1997), olfactory threshold tests are based on alternative forced-choice procedures consisting of distinguishing between stimulations with and without odors (target vs. non-target) in random temporal order. In other words, the participant must remember and compare each stimulus before identifying the target among two or three non-targets. Thus, to pass the test, one solution is to use a cognitive strategy based on the ability to detect non-targets and thus guess the stimulation that is the target. Interestingly, one study from the present meta-analysis (Dulay et al., 2005)

included a two-alternative forced choices method instead of a three-alternative forced choices method, and showed smaller effect sizes, which could suggest a lower cognitive load compared to a three-alternative forced choices method.

Furthermore, the use of alternative olfactory detection tests designed to have minimal memory or cognitive impact (Doty & Laing, 2015) could test this first hypothesis. Signal detection tests are good candidates, as they are based on a non-forced choice procedure (i.e. participants are asked to determine whether the stimulus presented is detectable or not, without having to directly compare it with another one previously presented, e.g. Doty et al., 1981) and account for the subject's response criterion in reporting the detection of an odor or not (liberalism vs. conservatism) (Doty et al., 1981; Doty & Laing, 2015). In the present meta-analysis, however, none of the included studies used a signal detection test to assess olfactory threshold detection. Future studies involving patients with cognitive disorders should keep that potential bias in mind when assessing the olfactory detection threshold in these populations.

The positive association between olfactory detection threshold and declarative memory performances may alternatively be explained by (2) the effect of age on brain regions that are common to both declarative memory and olfaction (Baltes & Lindenberger, 1997; Dulay & Murphy, 2002). Aging effects on hippocampal and prefrontal regions (Bartsch & Wulff, 2015; Bettio et al., 2017) could play a mediator role in the relationship between olfactory detection threshold and declarative memory

performance, as both regions are involved in odor detection (Igarashi et al., 2014; Murphy et al., 2003; Potter & Butters, 1980; Steffener et al., 2021; Zhang et al., 2019) and memory functioning (Borders et al., 2022; Cabeza et al., 2002; Melrose et al., 2020; Sexton et al., 2010). Future neuroimaging studies should evaluate the potential mediating effect of hippocampal and prefrontal cortex volume on the relationship between odor detection threshold and declarative memory.

Meta-regressions showed that age moderates the relationship between olfactory detection threshold and memory performance in older adults, as the relationship is stronger in advanced age. The effect of age on the relationship can be explained by the fact that these two capacities are especially weakened by the aging process. Normative data suggest that olfactory detection thresholds are most sensitive to aging compared to other olfactory functions (Hummel et al., 2007; Oleszkiewicz et al., 2019). The same phenomenon is found with memory, as episodic memory is the type of long-term memory that is the most sensitive to aging, while semantic memory is mostly preserved (Nyberg et al., 2003, 2012; Rönnlund et al., 2005). Again, age-related damages to medial-temporal lobe structures have been associated with both worse declarative memory and olfactory detection threshold performance in healthy older adults. More specifically, levels of tau and β-amyloid aggregations in the brain are associated with atrophy of medial-temporal lobe structures and worse declarative memory in cognitively normal older adults compared to young adults (Marks et al., 2017), while olfactory detection threshold performance has been associated with a smaller volume of the hippocampus and other

medial-temporal structures, such as the amygdala and the entorhinal cortex, in healthy older adults (Murphy et al., 2003).

Our study has certain limitations. First, there was heterogeneity regarding tests that were included. With regards to the olfactory tests, a majority of included correlations were performed using validated tests such as the Sniffin' Sticks Test (Hummel et al., 1997, 2007), the University of Pennsylvania Smell Identification Test (UPSIT, Doty et al., 1984), the Scandinavian Odor-Identification Test (Nordin et al., 1998), and the 12-item Cross-Cultural Smell Identification Test (Doty et al., 1996), while others used equivalent experimental tests. Similarly, regarding memory tests, we only included similar and comparable tests (episodic memory: free immediate and delayed recalls of word list learning; semantic memory: categorial fluency, denomination, general knowledge, and vocabulary tasks). When heterogeneity was found in different effect sizes, we analyzed correlation effect sizes for each subcategory of memory tests. Further, this meta-analysis does not include other cognitive domains that may influence olfactory scores, such as working memory (Dulay et al., 2008; Hedner et al., 2010; Tonacci et al., 2017). Another limitation is the small number of studies that assessed the relationship between olfactory detection threshold and declarative memory ($k = 5$ for episodic memory; $k = 7$ for semantic memory). Therefore, our results must be interpreted carefully. Finally, by design, this meta-analysis only included studies with linear correlation effect sizes between olfactory and memory performance in cognitively normal older adults. Other studies may have included data relating to olfactory and memory performance in this population, but

did not show correlational effect sizes, which prevented us from including them in the present meta-analysis.

Conclusion

Olfactory identification and olfactory detection threshold are related to declarative memory in cognitively normal older adults. These results suggest that both olfactory performances are related to verbal declarative memory but remain distinct from it. Finally, age moderates the association between olfactory detection threshold and memory performance.

Conflict of Interest

The authors declare no conflict of interest.

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Data Availability

This meta-analysis used accessible data from different published studies. This study was not preregistered.

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Article scientifique 5

The Predictive Role of Olfactory Identification on Episodic Memory and Mild Cognitive Impairment: Results from the CIMA-Q Cohort

The Predictive Role of Olfactory Identification on Episodic Memory and Mild Cognitive Impairment: Results from the CIMA-Q Cohort[1]

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Abstract

Background: Olfactory identification impairment can be an early clinical marker of Alzheimer's disease, detectable even at the mild cognitive impairment (MCI) stage. While olfactory identification is associated with episodic memory functioning, its predictive power for overall cognitive performance remains unclear. **Objective:** This study aimed to (1) assess the predictive value of olfactory identification for episodic memory functioning, and (2) assess the role of olfactory identification in discriminating between MCI and individuals with subjective cognitive decline (SCD). **Methods:** We used the University of Pennsylvania Smell Identification Test (UPSIT) to assess olfactory function in 48 participants with SCD (mean age: 75.82, SD: 5.64) and 45 with MCI (mean age: 80.08, SD: 5.86) from the CIMA-Q cohort. We evaluated episodic memory using the Rey Auditory Verbal Learning Test (RAVLT). LASSO regression models were fitted, with 80% of the data used for training and 20% for testing. **Results:** UPSIT scores were associated with both total ($\beta = 0.45$, $p = 0.03$) and delayed recall scores ($\beta = 0.18$, $p = 0.02$), independently of diagnosis. Including UPSIT in predictive models increased the explained variance for RAVLT total recall from 9% to 19% and for delayed recall from 8% to 20%. The MCI group exhibited significantly lower UPSIT scores compared to the SCD group ($p = 0.01$); Linear Discriminant Analysis demonstrated moderate accuracy (69%) for distinguishing groups, with higher specificity (79%) to rule out MCI than sensitivity (58%) for detecting it. **Conclusions:** Olfactory identification is a valuable addition to cognitive screening as it enhances the prediction of episodic memory function. It represents a potential low-cost, non-invasive screening tool for cognitive decline.

Keywords: Olfactory identification; Episodic memory; Subjective cognitive decline; Mild cognitive impairment; Alzheimer's disease.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by a slow and progressive accumulation of neurofibrillary tau and β-amyloid depositions occurring over decades (Bateman et al., 2012; Jack, Wiste et al., 2018; Jack, Bennett et al., 2018; Jia et al., 2024; Villemagne et al., 2013). These depositions initially accumulate in key structures such as the hippocampus, parahippocampal gyrus, and entorhinal cortex ultimately leading to cognitive impairments (Gabrieli et al., 1997; Squire & Zola, 1991; Maass et al., 2018; Aschenbrenner et al., 2018; Marks et al., 2017), with episodic memory—responsible for the recall of personal experiences and events—typically being the first cognitive domain to be impaired at the mild cognitive impairment (MCI) stage of the disease (Maass et al., 2018; Albert et al., 2011; Petersen et al., 1999; Mormino et al., 2009). In individuals with subjective cognitive decline (SCD)—the stage preceding MCI where individuals perceive cognitive decline despite objective cognitive performance within normal limits (Jessen et al., 2014, 2022)—hippocampal volume is associated with episodic memory performance; this is not the case in cognitively healthy older adults (Caillaud et al., 2019).

While SCD and MCI are risk factors for further cognitive decline and AD (Janssen et al., 2021; Pavisic et al., 2021; Wen et al., 2022; Boyle et al., 2006), these populations are heterogeneous, and not all individuals progress to dementia or test positive for tau and amyloid biomarkers. Approximately 12% of individuals under 75 with SCD progress to MCI or dementia, rising to 28% among those over 75 (Liew, 2020). Positivity for AD

biomarkers in SCD varies widely, from 10% to 76% (Ebenau et al., 2020; Jansen et al., 2022; Wolfsgruber et al., 2019). Annual conversion rates from MCI to AD dementia range from 7.5% to 16.5%, with about half testing negative for AD biomarkers (Petersen et al., 2013; Rabinovici et al., 2019). As treatments for AD advance and become more available (Mintun et al., 2021; Sims et al., 2023; van Dyck et al., 2023), we will increasingly need to better target at-risk individuals. Identifying other early clinical markers alongside SCD and MCI may improve the detection of individuals at higher risk for AD and cognitive decline.

Olfactory decline is an early clinical marker of AD (Murphy, 2019; Albers et al., 2006), especially involving odor identification and odor recognition impairments. This is in contrast to other neurodegenerative diseases, such as Parkinson's disease, which is characterized by a general olfactory impairment across olfactory tasks (Rahayel et al., 2012). Individuals with AD exhibit a more specific impairment in their ability to identify and recognize odors (Rahayel et al., 2012); the same is true for individuals with MCI (Roalf et al., 2017; Jung et al., 2019), and even individuals with SCD exhibit a trend toward lower olfactory identification (Jobin, Zahal et al., 2021). At the dementia and MCI stages of AD, olfactory processing areas in the medial temporal lobe (i.e., piriform cortex, entorhinal cortex, amygdala) are damaged (Jobin, Boller et al., 2021, 2023; Lu et al., 2019; Vasavada et al., 2015; Thomann et al., 2009), and olfactory identification scores are associated with regional tau accumulation within the medial temporal lobe (Klein et al., 2021; Risacher et al., 2017; Diez et al., 2024). Olfactory identification is associated with

hippocampal volume and entorhinal cortex thickness in patients with MCI (Dhilla Albers et al., 2016; Kose et al., 2021; Hagemeier et al., 2016; Kjelvik et al., 2014; Murphy et al., 2003; Yoshii et al., 2019; Yu et al., 2019) and individuals with SCD without cognitive impairment (Papadatos & Phillips, 2023).

In this context, it is important to highlight that odor identification and episodic memory are associated in older adults without cognitive impairment (Jobin, Roy-Côté et al., 2023), and both functions follow similar declining trajectories in aging (Dintica et al., 2021). When compared, patients with amnestic MCI exhibited lower olfactory identification than those with non-amnestic MCI (Park et al., 2018). A possible genetic underpinning for this is the ε4 allele of the Apolipoprotein E (ApoE) gene, a genetic risk factor for AD: in carriers, long-term episodic memory decline and odor identification impairment are correlated, which was not the case in non-carriers (Olofsson et al., 2016).

Olfactory testing could thus serve as a tool to screen for cognitive impairment in conditions such as preclinical AD (Jobin et al., 2025). In this study, we therefore aimed to assess the predictive power of olfactory identification testing on episodic memory performance in individuals at risk for AD. More specifically, we aimed to (1a) assess the relationship between olfactory identification and episodic memory performance; (1b) assess the predictive value of olfactory identification for episodic memory functioning; (2a) compare olfactory identification performance between participants with MCI and

those with SCD; and (2b) examine the ability of olfactory identification to discriminate between MCI and SCD.

Materials and Method

The study was conducted in accordance with the Declaration of Helsinki and received approval from the Ethics Committee at the *Institut universitaire de gériatrie de Montréal'*s research center. All participants gave written consent after a detailed explanation of the study.

Participants

Data for this research came from the Consortium for the Early Identification of Alzheimer's Disease–Quebec (CIMA-Q; Belleville et al., 2019), launched in 2013 with initial funding from Fonds de recherche du Québec – Santé (FRQS) and Pfizer. The primary aim of CIMA-Q is to establish a well-characterized cohort of older adults with comprehensive clinical, cognitive, neuroimaging, and blood-based profiles to (1) support early Alzheimer's disease diagnosis, (2) provide a well-characterized cohort for the scientific community, (3) identify new therapeutic targets to prevent or slow cognitive decline in Alzheimer's disease, and (4) facilitate future clinical studies. CIMA-Q is led at the Institut universitaire de gériatrie de Montréal, part of the Centre Intégré Universitaire de Santé et de Services Sociaux du Centre-sud-de-l'île de Montréal. The consortium represents a collaborative effort among Quebec researchers from Université Laval, McGill University, Université de Montréal, and Université de Sherbrooke.

Since 2014, CIMA-Q has recruited a longitudinal cohort of participants who are (1) cognitively normal, (2) with SCD, (3) with MCI, or (4) with Alzheimer's type dementia. In the current study, we included all eligible participants with SCD or MCI who underwent an olfactory examination between November 2022 and September 2024 (n = 93). All participants were community-dwelling older adults aged 65 or over, living independently in Montreal, Sherbrooke, and Quebec City in Canada. All participants underwent a comprehensive neuropsychological evaluation and were evaluated by expert physicians.

All recruitment procedures, clinical, cognitive, and neuropsychiatric measurements, and inclusion and exclusion criteria have been described previously (Belleville et al., 2019). Participants from the MCI group (Montreal Cognitive Assessment, MoCA; Nasreddine et al., 2005, score between 20 and 26) met the National Institute on Aging and the Alzheimer's Association (NIA-AA) clinical criteria for MCI (Albert et al., 2011): (1) a reported cognitive decline; (2) an objective cognitive impairment typically in episodic memory, (3) the preservation of independence in functional abilities, and (4) the absence of dementia. Participants from the SCD group (MoCA score ≥ 26) met the criteria of the Subjective Cognitive Decline Initiative (Jessen et al., 2014): (1) a reported cognitive decline, (2) cognitive performance within the normal range, (3) not meeting MCI criteria. Participants were excluded if they had significant neuropsychiatric comorbidities, neurological diseases (e.g., subdural hematoma, epilepsy, or non-Alzheimer's dementias), a history of intracranial surgery, active substance dependence, high-dose benzodiazepine

use, or any condition deemed likely to interfere with cognitive performance or study participation.

Design

The CIMA-Q project is a large-scale, multicenter, and longitudinal study with standardized cognitive and neuroimaging assessments (see http://www.cima-q.ca/ for more details). After a telephone-based pre-screening interview using the Mini-Mental State Examination (t-MMSE; Newkirk et al., 2004), all eligible participants underwent a clinical examination and a neuropsychological assessment, which included an olfactory assessment.

Episodic Memory Assessment

The Rey Auditory Verbal Learning Test (RAVLT) was used to assess episodic memory (Schmidt, 1996). In this task, a 15-item list of unrelated words was read to the participant across five trials, with the total number of recalled words recorded as the total recall score. Following an interference list, participants were asked to recall the original list immediately and again after a 30-minute delay, the latter providing a delayed recall score.

Olfactory Identification Assessment

The University of Pennsylvania Smell Identification Test (UPSIT) was used to measure olfactory identification (Doty et al., 1984). Participants were presented with a

series of odorants embedded in scratch-and-sniff booklets and had to identify the odor from a set of four choice options. The test consists of 40 items, and the score represents the total number of correctly identified odors. Lower scores indicate poorer olfactory function, which may be associated with various neurological conditions.

Statistical Analysis

To analyze the association between the UPSIT score and memory outcomes independently of diagnosis, we performed linear regression models. In each model, the RAVLT scores were the dependent variable, while diagnosis, age, sex, and education were included as covariates.

To analyze the predictive value of the UPSIT score on cognitive outcomes, we used the Least Absolute Shrinkage and Selection Operator (LASSO) regression models to identify significant predictors of cognitive outcomes. LASSO regression was chosen because it performs variable selection and regularization simultaneously, prevents overfitting and addresses multicollinearity. The target variables were RAVLT total and delayed recalls. For both scores, we computed two models. *Model 1* included age, sex, and education as predictors, while *Model 2* included age, sex, education, and UPSIT. The data were split into training and testing sets, with 80% of the data used to train the models and 20% reserved for testing. To optimize the models, we performed 10-fold cross-validation and selected the optimal value of the regularization parameter (lambda, λ) based on the lowest mean squared error (MSE) from these cross-validation runs. For each model,

we calculated the Root Mean Square Error (RMSE), R-squared (R^2), and Pearson's r to assess the linear relationship between predicted and actual values. The analysis was repeated across 1000 iterations, with different random splits of the data, to ensure robust and stable estimates of model performance and coefficients.

To compare UPSIT scores between participants in the SCD and MCI groups, we performed an ANCOVA with UPSIT score as a within-subject factor and groups as a between-subject factor. Education, sex and age were used as covariates.

To assess the ability of UPSIT to differentiate between SCD and MCI groups, we conducted a Linear Discriminant Analysis (LDA). The LDA model included UPSIT scores and demographic variables (age, sex, and education) as predictors to classify participants into the two diagnostic groups (SCD and MCI). Prior probabilities were calculated based on group proportions in the dataset, and the model estimated the group means for each predictor variable. The discriminant function coefficients were used to derive a linear combination of predictors that maximized the separation between the groups. Model performance was evaluated using overall classification accuracy, sensitivity (true positive rate for MCI), and specificity (true negative rate for SCD). We set the significance level (alpha) at 0.05 for all analyses.

Results

Characteristics of participants are presented in Table 1.

Table 1.

Characteristics of Participants

Variables	SCD $n = 48$ Mean (SD)	MCI $n = 45$ Mean (SD)	p-value
Age in years	75.82 (5.64)	80.08 (5.86)	**< 0.001**
Female/Male	34/14	22/23	0.051
Years of Education	7.67 (4.20)	6.67 (4.02)	0.25
MoCA (/30)	27.81 (1.35)	23.51 (1.94)	**< 0.001**
RAVLT total recall (/75)	50.04 (9.17)	40.91 (10.12)	**< 0.001**
RAVLT delayed recall (/15)	10.85 (2.61)	7.32 (3.86)	**< 0.001**
UPSIT (/40)	29.42 (6.13)	26.02 (6.49)	**0.01**

Note. MCI = Mild Cognitive Impairment; MoCA = Montreal Cognitive Assessment; RAVLT = Rey Auditory Verbal Learning Test; SCD = Subjective cognitive decline; SD = Standard deviation; UPSIT = The University of Pennsylvania Smell Identification Test.
Statistical T-test analyses indicated significant differences in age, cognitive, and olfactory measures (MoCA, RAVLT, UPSIT) between groups, with the MCI group exhibiting lower scores. No significant difference was found in sex distribution and years of education. RAVLT scores were missing for three participants.

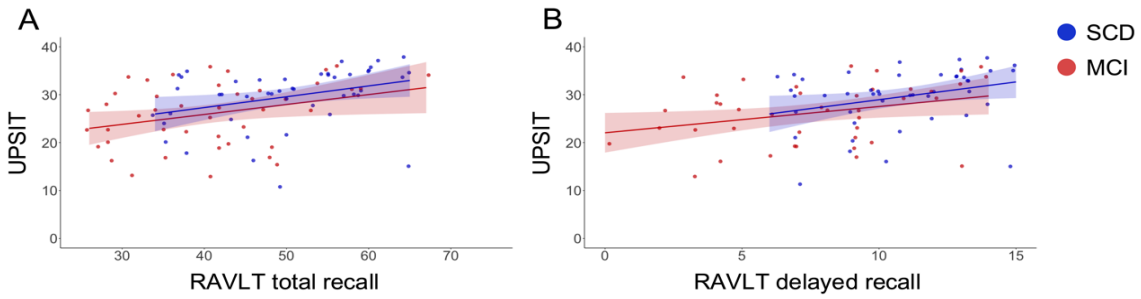
Associations Between the UPSIT Score and Episodic Memory

The *UPSIT* was significantly and positively associated with the *RAVLT total recall* ($\beta = 0.45$, $p = 0.03$). *Sex* ($\beta = -7.33$ (lower scores in males), $p < 0.001$) was also significantly associated with *RAVLT total recall*, while *age* ($\beta = 0.03$, $p = 0.85$) and *education* ($\beta = 0.25$, $p = 0.28$) were not. The interaction term between *UPSIT* and *diagnosis* was not significant either ($\beta = 0.07$, $p = 0.80$). The model accounted for 34% of the variance in the *RAVLT total recall* ($F[6, 83] = 8.84$, $p < 0.001$, adj. $R^2 = 0.35$); three observations were missing and were therefore not included in the model (see Figure 1).

Regarding delayed recall, the *UPSIT* was also significantly and positively associated with the *RAVLT delayed recall* ($\beta = 0.18, p = 0.02$). *Sex* (β = -2.06 (lower scores in males), $p = 0.004$) was also significantly associated with *RAVLT delayed recall*, while age ($\beta = 0.01$, $p = 0.84$) and education ($\beta = 0.04$, $p = 0.66$) were not. The interaction term between *UPSIT* and *diagnosis* remains non-significant (β = -0.04, $p = 0.68$). The model accounted for 33% of the variance in the RAVLT delayed recall score ($F[6, 83] = 8.40$, $p < 0.001$, adj. $R^2 = 0.33$); three observations were missing and not included in the model.

Figure 1.

Linear Associations Between UPSIT and RAVLT Scores



Note. Associations between UPSIT and RAVLT total and delayed recall scores, adjusted for diagnosis, age, sex, and education. Each plot includes a regression line with a shaded 95% confidence interval. A: UPSIT scores were positively associated with RAVLT total recall ($\beta = 0.45$, $p = 0.03$). B: UPSIT scores were positively associated with RAVLT delayed recall ($\beta = 0.18$, $p = 0.02$).

UPSIT Score as a Predictor of Episodic Memory

The LASSO regression models for each cognitive domain are reported in Table 2. *Model 1* explained 9% of the *RAVLT total recall* variance (RMSE = 10.41[CI: 10.35 – 10.48], adj. R^2 = .09 [CI: .08 – .09]), with *age* (β = -0.39) and *education* (β = 0.46) being

significant predictors, while the coefficient for *sex* was not retained after regularization. When *UPSIT* was included in the model, *Model 2* explained 19% of the *RAVLT total recall* variance (RMSE = 9.83 [CI: 9.76 – 9.91], adj. R^2 = .19 [CI: .14 – .20]), with *age* (β = -0.27), *education* (β = 0.38), and *UPSIT* (β = 0.55) being significant predictors, whereas *sex* remained non-contributory after regularization. The non-overlapping confidence intervals for adj. R^2 between *Models 1 and 2* suggest a meaningful contribution of olfactory identification to the models. RMSE (t = -22.45, $p \leq 0.001$) was significantly lower in Model 2, which included the UPSIT, with higher adj, R^2 (t = 20.89, $p \leq 0.001$).

Table 2.

Results of LASSO Regression Models for Predicting Episodic Memory Scores

Episodic memory scores	Predictors	ß	RMSE	R^2
	Model 1		10.41 [10.35 – 10.48]	.09 [.08 – .09]
	Intercept	73.11		
	Age	-0.39		
	Sex	.		
	Education	0.46		
RAVLT total recall	Model 2		9.83 [9.76 – 9.91]	.19 [.14 – .20]
	Intercept	48.90		
	Age	-0.27		
	Sex	.		
	Education	0.38		
	UPSIT	0.55		
	Model 1		3.72 [3.69 – 3.75]	.08 [.07 – .09]
	Intercept	18.92		
	Age	-.14		
	Sex	.		
	Education	.11		
RAVLT delayed recall	Model 2		3.49 [3.46 – 3.52]	.20 [.19 – .21]
	Intercept	11.41		
	Age	-.10		
	Sex	.		
	Education	.09		
	UPSIT	.18		

Note. For each RAVLT total and delayed recall score, two models were tested: Model 1 included age, sex, and education as predictors, while Model 2 added UPSIT score as an additional predictor. The table displays the mean metrics over 1000 iterations: standardized coefficients (β) for each predictor, Root Mean Square Error (RMSE), adjusted R-squared (R^2). Dots (.) represent coefficients not retained in the model after regularization. Numbers in brackets represent the 95% confidence intervals.

Regarding the *RAVLT delayed recall*, *Model 1* explained 8% of the variance (RMSE = 3.72 [CI: 3.69 – 3.75], adj. R^2 = .08 [CI: .07 – .09]), with *age* (β = -0.14) and *education* (β = 0.11) being significant predictors, while the coefficient for *sex* was not retained after regularization. When *UPSIT* was included in the model, *Model 2* explained 20% of the variance (RMSE = 3.49 [CI: 3.46 – 3.52], adj. R^2 = .20 [CI: .19 – .21]), with *age* (β = -0.10), education (β = 0.09), and *UPSIT* (β = 0.18) being significant predictors, whereas *sex* remained non-contributory after regularization. Again, the non-overlapping confidence intervals for adj. R^2 between *Models 1 and 2* suggest a meaningful contribution of olfactory identification to the models. RMSE (t = -21.02, $p \leq 0.001$) was significantly lower in Model 2, which included the UPSIT, with higher adj, R^2 (t = 18.78, $p \leq 0.001$).

UPSIT Score Comparison Between SCD and MCI Groups

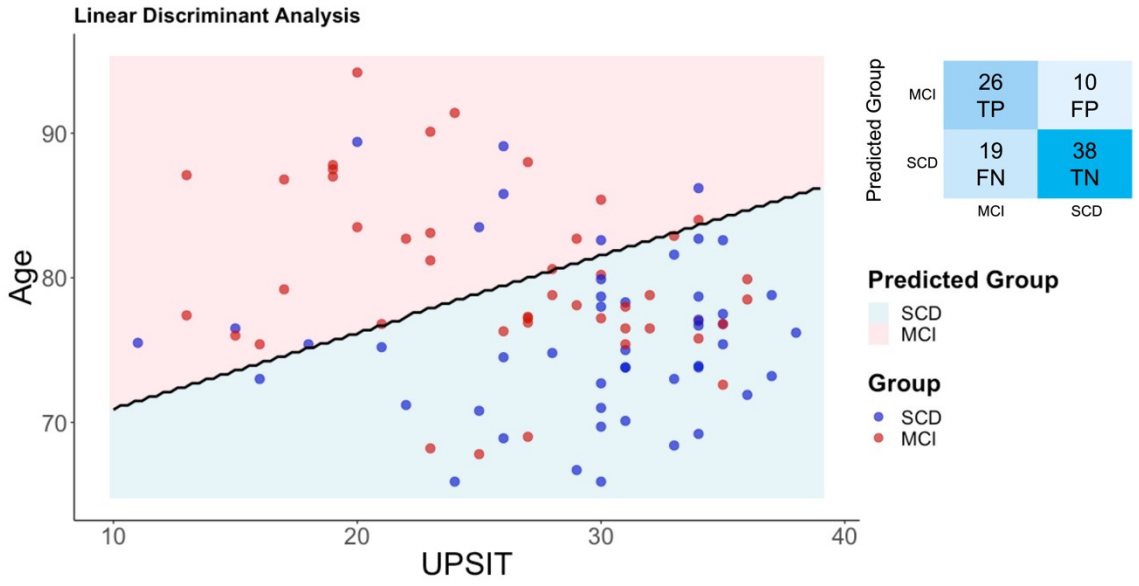
When comparing UPSIT scores between SCD and MCI groups, an ANCOVA revealed a significant effect of *group* demonstrating significantly lower scores in the MCI group compared to the SCD group (F[1, 85] = 6.75; p = 0.01; η^2p = 0.07). Main effects of *age* (F[1, 85] = 2.06; p = 0.15; η^2p = 0.02), *sex* (F[1, 85] = 0.02; p = 0.89; η^2p < 0.001), and *education* (F[1, 85] = 0.57; p = 0.45; η^2p < 0.001) were not significant, nor were interaction terms between *groups* and *age* (F[1, 85] = 1.90; p = 0.17; η^2p = 0.02), *groups* and *sex* (F[1, 85] = 0.003; p = 0.96; η^2p < 0.001), and *groups* and *education* (F[1, 85] = 1.72; p = 0.19; η^2p = 0.02).

Group Discrimination Using UPSIT Score

LDA indicated that *UPSIT* scores (-0.066), *age* (0.125), *sex* (0.612), and *education* (-0.096) contributed to the discriminant function. The model classified participants into their respective groups with an overall accuracy of 69%. Sensitivity (true positive rate for MCI) was 58%, indicating that the model correctly identified 58% of individuals in the MCI group. Specificity (true negative rate for SCD) was 79%, reflecting a higher ability to classify SCD participants correctly. Among the 45 MCI participants, 26 were correctly classified as MCI (true positives), while 19 were misclassified as SCD (false negatives). Conversely, among the 48 SCD participants, 38 were correctly identified as SCD (true negatives), while 10 were misclassified as MCI (false positives). The decision boundary plot (see Figure 2) demonstrates the separation between the SCD and MCI groups based on the predictors.

Figure 2.

Linear Discriminant Analysis of UPSIT Scores and Age to Differentiate Between SCD and MCI Groups



Note. The scatter plot illustrates the distribution of SCD (blue dots) and MCI (red dots) participants based on UPSIT scores and age, with the black line representing the Linear Discriminant Analysis decision boundary. The shaded areas indicate predicted group classification: pink for MCI and blue for SCD. The confusion matrix summarizes classification results: true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN). The model achieved 69% accuracy, with sensitivity (MCI detection) of 58% and specificity (SCD detection) of 79%.

Discussion

In this study, we aimed to assess the predictive power of olfactory identification on episodic memory performance in individuals at risk for AD. We used a data-driven approach to investigate its predictive value on episodic memory performance and LDA to evaluate the utility of olfactory identification in distinguishing between SCD and MCI. Our findings revealed that olfactory identification was associated with RAVLT total recall and delayed recall scores, independently of diagnosis. Including UPSIT scores in

predictive models significantly enhanced the explained variance from 9% to 19%, and from 8% to 20% for total recall scores and delayed recall scores, respectively. In terms of group comparisons, olfactory identification was significantly lower in individuals with MCI compared to those with SCD. Using the olfactory identification score within Linear Discriminant Analysis demonstrated moderate accuracy (69%) in distinguishing between SCD and MCI groups, with a lower sensitivity (58%) for detecting MCI than specificity for identifying SCD (79%). This indicates that the model was more effective at excluding MCI based on olfactory performance than identifying it within the CIMA-Q cohort.

Our results showed significant associations between olfactory identification and episodic memory scores, independently of diagnosis. Thus, we demonstrated that olfactory identification is associated with episodic memory, replicating findings from the literature (Papadatos & Phillips, 2023). Using a data-driven approach, we quantified the predictive value of olfactory identification scores on cognitive and episodic memory performance across all participants. LASSO models included UPSIT scores as significant predictors of RAVLT scores. When combined with demographic information from our participants, olfactory identification scores improved the explained variance for episodic memory scores. These results support the suggestion of using olfactory identification testing as an additional measurement for MCI screening (Jobin et al., 2025) and episodic memory performance in participants at risk for AD. Interestingly, episodic memory testing is the best predictor of AD dementia among cognitive measurements (Belleville et al., 2017); with amnestic MCI patients being at higher risk of developing AD dementia

compared to those with the non-amnestic presentation (Mitchell & Shiri-Feshki, 2009; Vos et al., 2013).

The common cause hypothesis (Baltes & Lindenberger, 1997; Dulay & Murphy, 2002) might explain the relationship between olfactory identification and episodic memory performance in participants at risk of AD, suggesting that the association between both functions results from underlying damages in common key areas (i.e., the hippocampus and entorhinal cortex) (Gabrieli et al., 1997; Squire & Zola, 1991; Hummel et al., 2010; Kjelvik et al., 2021; Lundström et al., 2011; Squire & Zola, 1996; Zald & Pardo, 2000). These brain regions are among the first damaged in AD pathology (Braak & Braak, 1991), and olfactory identification scores have been associated with cross-sectional (Klein et al., 2021; Risacher et al., 2017) and longitudinal tau accumulation in these central olfactory areas (Diez et al., 2024). Several studies have shown a relationship between olfactory identification and the morphometry of the hippocampus and entorhinal cortex in CN older adults (Dhilla Albers et al., 2016; Devanand et al., 2010), individuals with SCD (Papadatos & Phillips, 2023), and patients with cognitive impairments associated with AD (Lu et al., 2019; Jobin et al., 2021; Hagemeier et al., 2016; Kjelvik et al., 2014; Murphy et al., 2003; Yoshii et al., 2019; Yu et al., 2019).

Future studies will aim to validate this model of the common cause hypothesis, as well as the predictive role of olfactory measurements on medial-temporal lobe damages,

by analyzing the shared variance explained by these damages on both episodic memory and olfactory decline, to elucidate the mechanisms underlying their relationship.

Our results are consistent with existing literature on impaired olfactory identification in MCI (Roalf et al., 2017; Jung et al., 2019). Furthermore, the LDA showed moderate accuracy (69%) in distinguishing between SCD and MCI groups, though its sensitivity for detecting MCI was lower than its specificity for identifying SCD. Clinically, among patients reporting cognitive decline, a higher olfactory identification score would be indicative of the absence of objective cognitive impairment (79%). In contrast, a lower olfactory score is less effective for screening MCI, with a sensitivity of 58%, indicating a need for further examination. These findings align with the understanding that while olfactory impairment is a recognized marker of AD (Murphy, 2019; Albers et al., 2015), not all individuals with MCI progress to dementia, and only approximately half test positive for AD biomarkers (Petersen et al., 2013; Rabinovici et al., 2019). Furthermore, olfactory identification impairment is not exclusive to AD; reduced olfactory function can result from a variety of other conditions, including sinusitis, COVID-19, head trauma, and nasal polyps, among others, which is to consider when interpreting the result of this study and in general clinical settings (Patel et al., 2022). These considerations underscore the need for a comprehensive approach when interpreting olfactory identification scores in clinical and research contexts, recognizing their utility as part of a broader diagnostic framework rather than as a standalone diagnostic tool.

Subjective cognitive decline plus or "SCD+" is a subcategory of SCD that includes other risk factors for cognitive decline such as a subjective decline specifically in memory, an onset of SCD within the past 5 years, being 60 years and older, a concern associated with SCD, a persistence of SCD over time, seeking medical attention, and a confirmation of cognitive decline by an observer (Jessen et al., 2014; Jessen et al., 2020). These additional features aim to better characterize individuals with SCD as having an elevated risk of developing an objective cognitive decline. Olfactory identification is associated with AD biomarkers in the medial temporal lobe (Klein et al., 2021; Risacher et al., 2017; Diez et al., 2024), long-term memory decline in ApoE ε4 gene carriers (Olofsson et al., 2016), and the conversion to AD dementia stage (Conti et al., 2013; Roberts et al., 2016; Wheeler & Murphy, 2021). Future longitudinal studies should aim to assess the longitudinal prediction of episodic memory decline in individuals with SCD using olfactory identification scores.

This study has certain limitations. Although we cross-validated our predictive models by using an 80/20% split within our sample, the sample size was relatively small and drawn from a single cohort (CIMA-Q). Another limitation is that most participants were recruited from the community, suggesting that they may have had milder impairments and a lower likelihood of progressing to dementia compared to patients from memory clinics (Farias et al., 2009; Slot et al., 2019). It is possible that the observed effects could be even stronger in a memory clinic population.

To conclude, the results of this study showed that olfactory identification is specifically associated with episodic memory and enhances its prediction in individuals at risk of AD. LDA showed higher specificity (79%) for identifying SCD than sensitivity (58%) for detecting MCI. These findings highlight olfactory identification as a potential low-cost marker for cognitive screening, better suited to ruling out MCI than detecting it. Future studies should validate these results in larger, diverse samples and explore its integration with advanced biomarkers for AD.

Author Contributions

B.J.: Conceptualization; data curation; formal analysis; investigation; methodology, project administration; visualisation; writing—original draft. N. P.: Funding acquisition; resources, methodology, supervision; writing - review & editing. J.F.: Conceptualization; funding acquisition; resources, methodology, supervision, writing—review & editing. B.B.: Conceptualization; funding acquisition; resources, methodology, supervision; writing—review & editing.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability

The data supporting the findings of this study are available on request by contacting the CIMA-Q http://www.cima-q.ca/

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Discussion générale

L'objectif principal de cette thèse était de caractériser l'état du système olfactif central chez les personnes âgées à risque de développer le trouble neurocognitif majeur lié à la MA ainsi que sa relation avec le fonctionnement de la mémoire déclarative au sein de cette population. Pour répondre à ces questions, nous avons utilisé l'imagerie par résonance magnétique (IRM) structurelle ainsi que des mesures olfactives et mnésiques sur différents groupes de personnes âgées à risque de développer la MA. Nous avons également réalisé trois méta-analyses afin de répondre à différents aspects de cette question. Globalement, cette thèse démontre le système olfactif central est endommagé au stade de TCL, plus précisément au niveau des régions limbiques et temporaux-médiales. Sur le plan comportemental, une tendance pour une plus faible capacité à identifier les odeurs a été observée au stade de DCS. Finalement, sur le plan cognitif, les mesures structurelles comme les mesures comportementales du système olfactif central ont été corrélées aux scores de mémoire déclarative. Le score d'identification olfactive permet d'améliorer la prédiction du fonctionnement de la mémoire épisodique et de mieux distinguer les personnes avec un TCL d'un DCS.

Plus précisément, l'objectif de l'étude 1 était d'effectuer différentes revues systématiques et méta-analyses afin de comparer le volume des structures du bulbe olfactif et du cortex olfactif primaire entre les personnes âgées avec trouble neurocognitif majeur lié à la MAA, avec TCL, et les personnes âgées sans trouble cognitif. Nous avons confirmé

la présence de fortes tailles d'effets pour une atrophie des deux régions au sein du trouble neurocognitif majeur, mais avec des résultats mitigés et défis méthodologiques pour l'analyse au stade de TCL.

Afin de pallier ces défis méthodologiques, dans le cadre de l'étude 2, nous avons spécifiquement analysé le système olfactif central aux stades précoces de la MA à l'aide de l'IRM. Basés sur des travaux de neuroimagerie fonctionnelle, nous avons créé des masques cérébraux originaux permettant pour la première fois une analyse des sous-régions « olfactives » des structures impliquées dans le traitement olfactif. Cette étude démontre des réductions de volumes spécifiques à ces sous-régions olfactives au sein des régions limbiques et médio-temporales du système olfactif central, c'est-à-dire le cortex piriforme, l'amygdale, le cortex entorhinal et l'hippocampe gauche, chez des individus avec un TCL. Ces réductions volumétriques n'ont pas été observées lorsque l'entièreté de ces structures, ou leurs sous-régions « non-olfactives », étaient comparées entre le groupe de personnes âgées avec TCL et les groupes sans troubles cognitifs. De plus, le volume de la sous-région olfactive de l'hippocampe gauche a été lié au score de mémoire épisodique.

Au sein de l'étude 3, nous souhaitions évaluer de manière comportementale l'état du système olfactif central au stade de DCS. En recensant toutes les études comparant l'identification olfactive des personnes âgées avec et sans DCS, nous avons trouvé une tendance pour une plus faible performance olfactive chez les personnes âgées avec DCS.

Dans le cadre de l'étude 4, nous avions comme objectif de mesurer l'association entre différentes fonctions olfactives (détection et identification des odeurs) et la mémoire déclarative (épisodique et sémantique) chez les personnes âgées sans trouble cognitif. Nous avons trouvé des associations significatives et similaires entre les différents scores olfactifs et les scores de mémoire déclarative; associations de faible amplitude. De plus, seulement l'association entre les scores de détection des odeurs et de mémoire déclarative était modérée par l'âge.

Finalement au sein de l'étude 5, nous avons comparé la capacité d'identification olfactive entre deux groupes de personnes âgées avec DCS et avec TCL. Nous avons également évalué la valeur prédictive des scores d'identification olfactive sur le fonctionnement en mémoire épisodique au sein de ces individus à risque de MA. Le score olfactif était plus faible au sein du groupe TCL comparativement au groupe DCS. Après avoir confirmé la relation linéaire entre les scores d'identification olfactive et les scores de rappel total immédiat et différés d'apprentissage d'une liste de mots, indépendamment du diagnostic de DCS ou TCL, un modèle d'apprentissage automatique a démontré que l'ajout de score d'identification olfactive dans les modèles prédictifs augmente significativement la variance expliquée pour les scores de rappel total immédiat de 9 à 19 % et de 8 à 20 % pour le score de rappel différé. Finalement, une analyse discriminante linéaire a démontré une précision modérée (69 %) pour distinguer les groupes DCS et TCL, avec une sensibilité plus faible (58 %) pour détecter le TCL par rapport à une spécificité plus élevée pour identifier le DCS (79 %). Autrement dit, le score

d'identification olfactive était plus efficace pour exclure le diagnostic de TCL que pour le détecter au sein de la cohorte CIMAQ.

Caractérisation des dommages au système olfactif central au stade de TCL

Les atrophies du bulbe olfactif au stade de trouble neurocognitif majeur de la MA, et des régions limbiques et médio-temporales du système olfactif central (c'est-à-dire le cortex piriforme, l'amygdale, le cortex entorhinal et l'hippocampe) retrouvées au sein des différentes études de cette thèse peuvent être associées aux dommages causés par la pathologie Alzheimer. Ces régions olfactives sont parmi les premières à être endommagés par les enchevêtrements neurofibrillaires (pathologie tau) (Braak & Braak, 1991; Kovács et al., 2001; Lowe et al., 2020; Therriault et al., 2022), qui prédisent l'atrophie cérébrale mesurée par IRM (Du et al., 2004; Gordon et al., 2018; La Joie et al., 2020; LaPoint et al., 2017; Pennanen et al., 2004; Whitwell et al., 2007, 2008).

Sur le plan structurel, un modèle propose également que ces structures du système olfactif central soient atteintes très tôt dans la maladie, dès l'âge adulte avec l'hippocampe et l'amygdale comme régions les plus précocement et sévèrement touchées par l'atrophie, suivie temporellement et en termes de sévérité, le cortex entorhinal et parahippocampique. Cette progression s'étend ensuite à d'autres zones, notamment les régions temporales, le striatum, le thalamus, ainsi que le cortex frontal moyen, le cortex cingulaire, pariétal et insulaire (Planche et al., 2022). Notre méthodologie a permis d'obtenir des résultats concordant avec les deux modèles de progression de la taupathologie (Braak &

Braak, 1991) et de l'atrophie structurelle (Planche et al., 2022). Nos études ont démontré des es réductions volumétriques de matière grise de sous-régions olfactives répondant à la stimulation olfactive de régions limbiques et médio-temporales (le cortex piriforme, l'amygdale, le cortex entorhinal et l'hippocampe gauche) chez des individus au stade de TCL, effets non retrouvés lorsque l'entièreté de ces structures était comparée avec des groupes cognitivement normaux ou avec DCS. Autrement dit, les résultats de cette thèse concordent avec les modèles préexistants, en avançant l'hypothèse que les sous-régions « olfactives » de ces structures soient plus sévèrement endommagées chez des individus au stade de TCL de la MA.

La morphométrie de ces régions a été associée à la performance en identification olfactive chez les individus à risque de MA (Chen et al., 2021; Dhilla Albers et al., 2016; Dong et al., 2023; Kjelvik et al., 2021; Murphy et al., 2003; Papadatos & Phillips, 2023; Tian et al., 2023). Les dommages spécifiques de la MA à ces régions limbiques et médio-temporales olfactives pourraient expliquer le trouble de l'identification associé à la maladie. Une étude récente a permis de confirmer certaines de ces hypothèses. En adoptant un devis longitudinal et multimodal, combinant des mesures d'identification olfactive, des acquisitions en TEP (tau et amyloïde) et des données de neuroimagerie structurelle, des chercheurs ont exploré la progression spatio-temporelle de la pathologie tau au sein du système olfactif central chez des individus sans trouble cognitif et au stade de TCL (Diez et al., 2024). L'étude a confirmé que les scores d'identification olfactive sont corrélés à l'accumulation de tau observée dans le cortex piriforme, le noyau olfactif

antérieur, l'amygdale et le cortex entorhinal. De plus, ces associations demeurent statistiquement significatives après ajustement pour les niveaux d'amyloïde, renforçant l'hypothèse que la pathologie tau est un facteur clé du déclin olfactif. L'aspect longitudinal de l'étude a démontré que de plus faibles scores en identification olfactive prédisaient une progression accélérée de l'accumulation de tau dans ces régions.

En parallèle, en utilisant une approche basée sur la théorie des graphes et des données longitudinales en TEP, ces travaux ont démontré que les structures du lobe temporal médial, telles que l'amygdale et le cortex entorhinal, jouent un rôle central dans la propagation de la pathologie tau vers les régions olfactives, notamment le cortex piriforme. Les projections provenant du locus coeruleus, transitant par le noyau du raphé et atteignant les régions trans-entorhinales, ont également été associées aux performances olfactives et pourraient refléter un mécanisme sous-jacent de propagation de la pathologie tau depuis le tronc cérébral vers le lobe temporal médial. Ces observations suggèrent que le système olfactif accumule la pathologie en tant que cible, recevant la pathologie des régions médio-temporales et/ou du tronc cérébral, plutôt que d'agir comme point de départ de la propagation via les voies olfactives périphériques. Dans une perspective clinique, il serait possible que le score en identification olfactive reflète les premiers dommages de la MA au sein du réseau olfactif central, et ce, à un stade préclinique avant l'apparition du TCL. La performance olfactive pourrait être un indicateur de la santé cérébrale et cognitive des individus à risque de MA.

Apparition du déclin olfactif aux stades précliniques

Sur le plan comportemental, les résultats de cette thèse suggèrent que le trouble de l'identification des odeurs serait significatif au stade de TCL, avec un début du déclin lors du stade DCS. Depuis la publication de la méta-analyse comparant l'identification olfactive des personnes âgées avec et sans DCS, démontrant une tendance pour un score plus faible chez ceux avec DCS, d'autres études ont comparé ces groupes. Trois études ont démontré de plus faibles scores chez le groupe DCS comparativement au groupe sans DCS (Bouhaben et al., 2024; Chen et al., 2021; Wang et al., 2021), alors qu'une autre étude n'a pas retrouvé cette différence significative (Papadatos & Phillips, 2023). Ces nouveaux résultats ajoutent du poids à cette hypothèse selon laquelle le déclin olfactif serait mesurable au stade de DCS de la MA.

Ces observations sont également appuyées par les données pathologiques mesurées chez des personnes âgées sans trouble cognitif. La pathologie tau a été mesurée de manière post-mortem au sein du bulbe olfactif chez des personnes âgées décédées sans trouble cognitif (Tremblay et al., 2022). Des observations similaires ont été effectuées de manière *in vivo* à l'aide de la TEP au sein du cortex olfactif primaire (Diez et al., 2024). Ces résultats appuient le modèle de Murphy proposé en 2019, selon lequel le déclin olfactif au sein de la MA débuterait avant l'apparition des troubles de mémoire épisodique au stade de TCL, en suivant la progression de la pathologie tau. Ainsi, la période de détection du déclin olfactif au sein de la MA serait au stade préclinique (Yang, 2024).

L'identification olfactive comme marqueur du fonctionnement de la mémoire épisodique

Les résultats de cette thèse suggèrent que l'utilisation du test d'identification olfactive dans un contexte de dépistage précoce de la MA pourrait être indicateur du fonctionnement de la mémoire épisodique, et donc de servir d'indicateur de la présence d'un TCL associé à la MA. Les résultats de l'étude 4 démontrent que, chez des personnes âgées sans trouble cognitif, le score d'identification olfactive est lié aux scores de mémoire épisodique. L'étude 5 a permis de démontrer qu'au sein de personnes âgées avec DCS et TCL, le score d'identification olfactive est prédictif du fonctionnement de la mémoire épisodique. La performance olfactive a également été plus faible chez le groupe avec TCL, répliquant les résultats de la littérature (Bouhaben et al., 2024; Jobin et al., 2024; Papadatos & Phillips, 2023; Risacher et al., 2017).

La littérature suggère que chez les personnes âgées sans trouble cognitif, la performance olfactive prédit le déclin cognitif général au long terme (Devanand et al., 2015; Dintica et al., 2019; Olofsson et al., 2020; Sohrabi et al., 2012; Windon et al., 2019) ainsi que la conversion au stade de TCL (Roberts et al., 2016; Wheeler & Murphy, 2021; Wilson et al., 2007). Les résultats de cette thèse démontrent plus spécifiquement que le score d'identification olfactive est lié à la mémoire déclarative, dont la mémoire épisodique chez des individus avec et sans trouble cognitif. Ces déclins seraient non seulement associés, mais parallèles au sein du vieillissement (Dintica et al., 2021). Chez des personnes âgées sans trouble neurocognitif majeur, le score olfactif a été associé au déclin au long terme de la mémoire épisodique et sémantique (Dintica et al., 2019). Ces

observations pourraient refléter un continuum entre vieillissement cognitif dit « normal » et vieillissement pathologique, dans la mesure où certaines personnes âgées présentant une cognition apparemment intacte peuvent être porteuses de biomarqueurs de la MA (Morris et al., 2018; Zhang et al., 2021). Autrement dit, l'association entre performance olfactive et mémoire déclarative chez les personnes âgées sans trouble cognitif manifeste pourrait signaler l'influence de processus neuropathologiques précoces, communs aux stades précliniques de la MA, notamment chez les individus présentant un DCS.

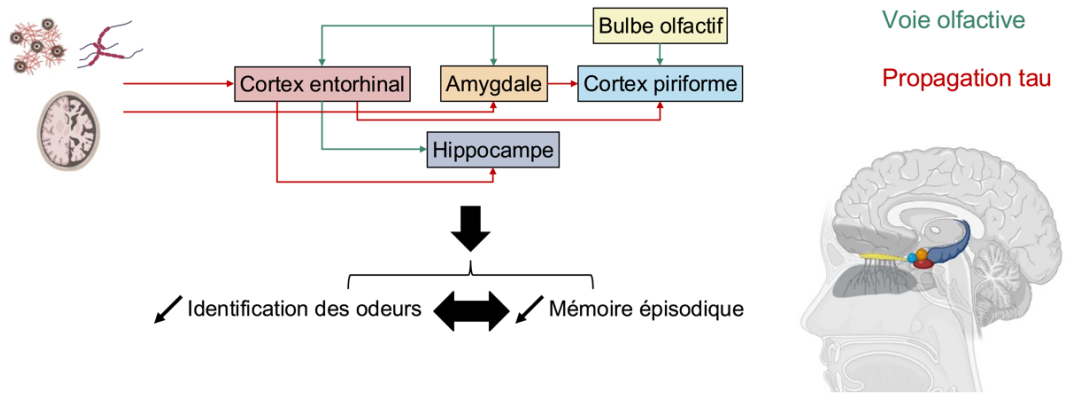
Appui à l'hypothèse des causes communes

Selon l'hypothèse des causes communes (Baltes & Lindenberger, 1997; Dulay & Murphy, 2002), la convergence de déclin olfactif et mnésique chez les personnes âgées est expliquée par des dommages à des structures cérébrales communes. Dans ce cas, les dommages seraient ceux de la MA, particulièrement de la neurodégénérescence causée par la propagation de la pathologie tau au sein du réseau olfactif primaire (Braak & Braak, 1991; Diez et al., 2024), qui inclut des régions mnésiques clés comme l'hippocampe et le cortex entorhinal. Les résultats de l'étude 2 ont pu appuyer cette hypothèse, en démontrant que le volume de la sous-région « olfactive » de l'hippocampe gauche est associé aux scores de mémoire épisodique chez un échantillon de personnes âgées à risque de MA. La mesure de l'identification olfactive pourrait donc refléter les premiers dommages au réseau mnésique, particulièrement au niveau de l'hippocampe et du cortex entorhinal comme les dommages à ces structures ont été associés au score d'identification olfactive (Chen et al., 2021; Dhilla Albers et al., 2016; Diez et al., 2024; Dong et al., 2023; Kjelvik

et al., 2021; Murphy et al., 2003; Papadatos & Phillips, 2023; Tian et al., 2023) (voir Figure 2).

Figure 2.

Dommages de la maladie d'Alzheimer sur le réseau olfactif



Note. Le schéma illustre l'impact de la pathologie tau sur le réseau olfactif primaire (bulbe olfactif, cortex piriforme, amygdale, cortex entorhinal) et secondaire (hippocampe). Les flèches rouges indiquent la propagation de la pathologie Alzheimer (tau), entrainant des dommages structuraux au sein de ces régions cérébrales. Selon l'hypothèse des causes communes, ces dommages expliquent la convergence des déclins olfactif et mnésique, et par conséquent, les associations observées entre les mesures d'identification olfactive et de la mémoire épisodique. La mesure d'identification olfactive pourrait donc être utilisée comme un indicateur du fonctionnement de la mémoire épisodique et des dommages cérébraux associés à la MA, en particulier au niveau du cortex piriforme, de l'amygdale, du cortex entorhinal et de l'hippocampe, qui sont des régions essentielles pour le fonctionnement olfactif et de la mémoire épisodique.

Appui au modèle de Larsson et al. (2016)

Larsson et al. (2016) avancent l'hypothèse selon laquelle l'identification olfactive serait mieux conceptualisée comme étant une forme de mémoire olfactive distincte, plutôt qu'une sous-catégorie de la mémoire sémantique. Bien que les scores aux tests d'identification olfactive soient corrélés avec ceux des tests de mémoire déclarative, et que ces fonctions reposent sur des bases neuroanatomiques communes, elles évalueraient des systèmes mnésiques distincts. Les études 4 et 5 de cette thèse soutiennent ce modèle en mettant en évidence des associations significatives, mais de faible à moyenne ampleur, entre les tests d'identification olfactive et ceux de mémoire déclarative. Ces résultats suggèrent donc que ces deux types de tests ne mesurent pas les mêmes mécanismes mnésiques. Bien que l'identification olfactive repose en partie sur les connaissances sémantiques (Larsson, 1997; Schab, 1991), elle mobilise également des processus cognitifs et neuroanatomiques propres à l'odorat en raison de connexions spécifiques et moins élaborées entre le cortex piriforme et les régions corticales impliquées dans les réseaux sémantiques (Arshamian & Larsson, 2014). Ces processus incluent l'imagerie olfactive et des interactions spécifiques entre le réseau olfactif et les circuits langagiers (Arshamian & Larsson, 2014; Olofsson et al., 2014). Ces particularités expliquent plusieurs particularités de la mémoire olfactive, notamment une analyse limitée des caractéristiques des odeurs comparativement aux stimuli visuels ou auditifs, une traduction sous-optimale des objets olfactifs en représentations lexicales, et une dégradation progressive de la qualité du signal olfactif à travers les étapes de traitement (Herz, 2005; Olofsson et al., 2013, 2014). Ainsi, la mémoire olfactive peut être considérée

comme un système distinct, façonné par les spécificités des structures responsables du traitement olfactif, en particulier le cortex piriforme.

Utilisation proposée du test d'identification olfactive chez les personnes âgées présentant un DCS

Considérant que les dommages au cortex olfactif primaire associés à la MA ainsi que le déclin olfactif apparaissent avant l'apparition du TCL, l'utilisation du test d'identification olfactive pour dépister précocement le risque de MA devrait se produire chez les individus rapportant un DCS. Tel que mentionné auparavant, la plainte d'un déclin subjectif de la mémoire est le premier symptôme cognitif de la MA (stade 2), mais ce ne sont pas sont pas tous les individus rapportant un DCS qui testent positifs aux biomarqueurs de la MA, avec proportion qui varie entre 10 et 76 % (Ebenau et al., 2020; Jansen et al., 2022; Janssen et al., 2021; Wolfsgruber et al., 2019), ni tous les individus qui progresseront vers des stades plus avancés de la maladie (Jessen et al., 2010; Liew, 2020; van Harten et al., 2018). Les résultats de cette thèse, ainsi que la littérature scientifique, démontrent que le test d'identification olfactive pourrait être sensible aux biomarqueurs avant l'apparition des troubles de mémoire épisodique au stade de TCL. Sur le plan cognitif, les résultats de cette thèse démontrent que le score olfactif peut être un indicateur du fonctionnement de la mémoire épisodique, le meilleur prédicteur cognitif de la conversion au stade de trouble neurocognitif majeur (Belleville et al., 2017). Ainsi, la mesure de l'identification olfactive pourrait être utilisée en clinique comme méthode de dépistage complémentaire à la plainte subjective de trouble de mémoire. Plus précisément, les résultats de l'étude 5 appuient l'indication selon laquelle un score en identification

olfactive élevé serait indicateur de l'absence de TCL, alors qu'un score faible ne serait pas nécessairement efficace afin d'indiquer le TCL. Autrement dit, le test d'identification olfactive est plus efficace pour exclure un TCL chez les individus rapportant des plaintes de trouble de mémoire (79 %) que pour le détecter (58 %).

Ce résultat modeste de détection du TCL peut s'expliquer par le fait que le trouble olfactif, comme la plainte de mémoire, est sensible, mais non spécifique à la MA. Plusieurs conditions peuvent altérer le système olfactif, dont d'autres maladies neurodégénératives comme les alpha-synucléinopathies comme la maladie de Parkinson et la démence à corps de Lewy, les traumatismes crâniens, les infections post-virales, les sinusites et l'anosmie congénitale (Patel et al., 2022). Ainsi, en contexte clinique, il serait indiqué d'utiliser le test olfactif selon l'algorithme suivant : un score élevé suggérerait une plus forte probabilité d'une absence de trouble cognitif, tandis qu'un score faible suggérerait la nécessité d'approfondir l'évaluation du patient à l'aide de ressources plus coûteuses en termes de temps ou financières. Ces ressources pourraient inclure une évaluation neuropsychologique et oto-rhino laryngologique, une IRM, une imagerie TEP, ainsi que l'analyse de biomarqueurs par prise de sang ou prélèvement de liquide céphalo-rachidien.

Trouble olfactif comme facteur du DCS+

Le *Subjective Cognitive Decline Plus* ou « DCS+ » désigne une sous-catégorie de DCS incluant des facteurs de risque supplémentaires de déclin cognitif visant à mieux différencier les individus présentant un DCS à risque élevé de progression vers un déclin

cognitif objectif (Jessen et al., 2014). Ces critères comprennent notamment la plainte subjective ciblée sur la mémoire, l'apparition du DCS dans les cinq dernières années, un âge de 60 ans ou plus, une inquiétude associée au DCS, une persistance de cette plainte dans le temps, une démarche active de consultation médicale, et une confirmation du déclin cognitif par un tiers (Jessen et al., 2014; Molinuevo et al., 2017).

L'intégration de scores faibles en identification olfactive comme facteurs du DCS+ pourrait contribuer à identifier les individus présentant un risque accru de déclin cognitif. Nos résultats et ceux de la littérature suggèrent que le déclin olfactif serait mesurable avant l'apparition du TCL et qu'il est associé aux biomarqueurs spécifiques de la MA (Diez et al., 2024; Klein et al., 2021; Lafaille-Magnan et al., 2017; Molinuevo et al., 2017; Reijs et al., 2017; Risacher et al., 2017), ainsi qu'aux mesures morphométriques de régions clés du fonctionnement mnésique comme l'hippocampe et le cortex entorhinal (Chen et al., 2021; Dhilla Albers et al., 2016; Dong et al., 2023; Kjelvik et al., 2021; Murphy et al., 2003; Papadatos & Phillips, 2023; Tian et al., 2023). Nos résultats suggèrent qu'il est prédictif de la performance en mémoire épisodique de manière transversale, alors que d'autres travaux ont démontré la valeur prédictive de la mesure olfactive et le déclin cognitif sur le plan longitudinal chez des individus sans trouble cognitif au temps de base (Devanand et al., 2015; Dintica et al., 2019; Olofsson et al., 2020; Sohrabi et al., 2012; Windon et al., 2019). La combinaison de deux facteurs de risques comme le trouble de l'identification olfactive et la plainte subjective de déclin cognitif pourrait améliorer la prédiction du déclin cognitif chez les individus à risque de MA, tout en renforçant l'intérêt

clinique de la plainte cognitive subjective comme outil de dépistage précoce simple, peu coûteuse et non invasive. De futures études longitudinales pourront examiner la capacité prédictive des scores d'identification olfactive en lien avec le déclin de la mémoire épisodique chez des individus rapportant un DCS. Une telle approche pourrait permettre d'affiner les stratégies de dépistage précoce et d'optimiser l'utilisation des ressources diagnostiques chez les individus les plus à risque de MA (p. ex., neuroimagerie, biomarqueurs sanguins ou du liquide céphalo-rachidien).

Limites et perspectives futures

Les limites de cette thèse doivent être prises en considération lors de l'interprétation des résultats et pour orienter les recherches futures. Tout d'abord, les devis transversaux utilisés ne permettent pas d'évaluer la prédiction à long terme du déclin cognitif chez nos participants. Les prochaines études devront intégrer suivi longitudinal pour mieux comprendre la valeur prédictive du trouble olfactif sur la progression vers des stades plus avancés de déclin cognitif. De plus, les devis utilisés dans cette thèse ne permettent pas d'inférer des liens de causalité, mais uniquement d'identifier des associations entre les mesures d'identification olfactive, les performances cognitives et les volumes cérébraux mesurés.

La majorité des participants de la cohorte CIMA-Q ont été recrutés au sein de la communauté. Ces individus, généralement moins atteints, présentent un risque plus faible de progression vers la MA que les patients provenant des cliniques de mémoire (Farias et

al., 2009; Slot et al., 2019). Par conséquent, il est possible que les effets observés dans cette thèse soient encore plus prononcés dans une population clinique. Enfin, bien que les participants inclus dans les études soient à risque de MA, ils ne présentaient pas de biomarqueurs confirmés de la maladie. Cette limite reflète néanmoins la réalité clinique, où les individus sont souvent évalués avant l'obtention de données des biomarqueurs tau et amyloïdes. L'intégration de biomarqueurs aurait cependant permis d'affiner les modèles et de renforcer la robustesse des conclusions.

Alors que l'atrophie du bulbe olfactif est bien documentée aux stades avancés de la MA, peu de données existent sur les modifications structurelles et fonctionnelles de cette région aux stades prodromaux de la MA. Les séquences d'IRM standards utilisées ne permettaient pas d'obtenir cette donnée qui aurait été pertinente pour enrichir les modèles proposés, comme le traitement olfactif central débute après le relai de l'information olfactive via les bulbes olfactifs. Étudier cette région avant l'apparition des troubles cognitifs au sein des stades précliniques permettrait de mieux caractériser la temporalité des dommages au système olfactif dans le décours de la maladie. De plus, cette thèse s'est limitée à l'analyse de données structurelles (matière grise) sans inclure d'analyses fonctionnelles. Étudier les aspects fonctionnels, par exemple à l'aide de l'IRM fonctionnelle, aurait permis de mieux développer les modèles proposés et d'approfondir la compréhension des mécanismes sous-jacents du trouble olfactif précoce au sein des individus à risque de MA.

Cette thèse s'est intéressée qu'à des processus spécifiques de la mémoire déclarative et olfactive. Étudier les interactions entre les différents mécanismes de mémoire épisodique (encodage, consolidation et récupération) et les fonctions olfactives de manière longitudinale permettrait de mieux comprendre l'évolution temporelle des déficits et la valeur prédictive du score d'identification olfactive sur ces différents mécanismes de mémoire épisodique. De plus, bien que les tests d'identification olfactive soient pertinents, ils ne mesurent qu'une portion des capacités olfactives humaines. L'ajout de différentes composantes olfactives comme la détection, la discrimination et la reconnaissance des odeurs, ou encore l'intégration de batteries numériques exécutables au domicile des participants comme l'*AROMHA Brain Health Test* (Jobin et al., 2025), pourrait permettre une évaluation plus complète et accessible, notamment pour des suivis à domicile.

Conclusion générale

Cette thèse visait à caractériser l'état du système olfactif central chez les personnes âgées à risque de développer la MA, en combinant des approches d'imagerie cérébrale, des analyses comportementales et des méta-analyses. Les résultats obtenus suggèrent que des dommages spécifiques au système olfactif central surviennent précocement dans l'évolution de la MA, dès les stades prodromiques de TCL, et que la tâche d'identification olfactive peut être un indicateur clinique pertinent pour le dépistage précoce de la maladie, notamment du déficit de mémoire épisodique associé.

Sur le plan neuroanatomique, cette thèse a démontré des réductions volumétriques spécifiques des sous-régions olfactives du cortex piriforme, de l'amygdale, du cortex entorhinal et de l'hippocampe gauche chez les individus au stade de TCL. Ces résultats concordent avec les modèles de progression de la pathologie tau et de l'atrophie structurelle liées à la MA, tout en mettant en lumière l'importance et la vulnérabilité des sous-régions « olfactives » de ces structures.

Sur le plan comportemental, les performances en identification olfactive se sont révélées diminuées au stade de TCL, avec une tendance suggérant un début du déclin au stade de DCS. Les associations observées entre les fonctions olfactives et la mémoire déclarative peuvent refléter des mécanismes partagés entre les systèmes mnésique et

olfactif. Ces associations suggèrent que le déclin olfactif est un reflet indirect des dommages neuroanatomiques et fonctionnels dans les réseaux olfactifs et mnésiques.

Enfin, cette thèse a démontré l'utilité potentielle de l'identification olfactive comme marqueur clinique. Les scores olfactifs augmentent la précision des modèles prédictifs pour distinguer les groupes DCS et TCL, ainsi que ceux basés sur l'apprentissage-automatique pour prédire la performance mnésique. Ces résultats suggèrent que les tests olfactifs pourraient jouer un rôle complémentaire dans le dépistage précoce de la MA et le suivi de la progression du déclin cognitif.

Cette thèse apporte des contributions importantes à la compréhension du trouble olfactif précoce liée à la MA, tout en mettant en lumière des méthodes innovantes, telles que l'analyse ciblée des sous-régions olfactives et l'intégration de données multimodales. Elle ouvre également la voie à de nouvelles recherches sur l'utilisation de tests olfactifs dans un cadre clinique pour les individus à risque de développer la MA.

À l'avenir, des études longitudinales combinant imagerie structurelle, fonctionnelle et mesures olfactives comportementales seront nécessaires pour approfondir notre compréhension des mécanismes reliant le déclin olfactif à la progression de la MA. De plus, l'intégration de données pathologiques, telles que la tau et l'amyloïde mesurées par TEP, pourrait permettre de mieux comprendre les liens entre pathologie cérébrale, fonctions olfactives et cognition.

En conclusion, cette thèse suggère que les dommages au système olfactif central constituent une signature précoce associé à la MA. Ces résultats renforcent l'idée que la performance en identification olfactive est un reflet de la santé cérébrale qui pourrait servir à mieux détecter et suivre la progression de cette maladie neurodégénérative.

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Appendice

Liste des publications externes à la thèse réalisées durant sa préparation

LISTE DES PUBLICATIONS EXTERNES À LA THÈSE RÉALISÉES DURANT SA PRÉPARATION

Fortier-Lebel, O., **Jobin, B.**, Lécuyer-Giguère, F., Gaubert, M., Giguère, J.-F., Gagnon, J.-F., Boller, B., & Frasnelli, J. (2021). Verbal episodic memory alterations and hippocampal atrophy in acute mild traumatic brain injury. *Journal of Neurotrauma*, *38*(11), 1506-1514. https://doi.org/10.1089/neu.2020.7475

Jobin, B., Magdamo, C., Delphus, D., Runde, A., Reineke, S., Soto, A. A., Ergun, B., Mukhija, S., Dhilla-Albers, A., & Albers, M. W. (2025). The AROMHA brain health test is a remote olfactory assessment to screen for cognitive impairment. *Scientific Reports*, *15*, Article 9290. https://doi.org/10.1038/s41598-025-92826-8

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Lécuyer Giguère, F., **Jobin, B.**, Robert, J., Bastien, L., Giguère, J.-F., De Beaumont, L., de Guise, E., & Frasnelli, J. (2020). Early parosmia signs and affective states predict depression and anxiety symptoms 6 months after a mild traumatic brain injury. *Chemical Senses*, *45*(6), 483-490. https://doi.org/10.1093/chemse/bjaa037

Nadeau, P. A., **Jobin, B.,** & Boller, B. (2023). Diagnostic sensitivity and specificity of cognitive tests for mild cognitive impairment and Alzheimer's disease in patients with down syndrome: A systematic review and meta-analysis. *Journal of Alzheimer's Disease, 95*(1), 13-51. https://doi.org/10.3233/JAD-220991

Zigrand, C., **Jobin, B.,** Lécuyer Giguère, F., Giguère, J.-F., Boller, B., & Frasnelli, J. (2022). Olfactory perception in patients with a mild traumatic brain injury: A longitudinal study. *Brain Injury, 36*(8), 985-990. https://doi.org/10.1080/02699052.2022.2109734