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CONSCIENCE DE SOI ET MÉMOIRE AUTOBIOGRAPHIQUE DANS LA MALADIE À CORPS DE LEWY :

ÉTUDE COMPORTEMENTALE ET EN NEUROIMAGERIE MULTIMODALE

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Tisserand A, Philippi N, Botzung A, Blanc F. Self in Dementia with Lewy bodies: a behavioral and multimodal neuroimaging study. *International Lewy Body Dementia Conference*, 15-18 juin 2022 (Newcastle upon Tyne, Royaume-Uni)

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Tisserand A, Blanc F, Muller C, Durand H, Demuynck C, Loureiro de Sousa P, Ravier A, Sanna L, Botzung A, Mondino M, Philippi N. Neuroimaging of autobiographical memory in dementia with Lewy bodies: a story of insula. Rencontres de la fondation Alzheimer, 7-8 décembre 2023 (Paris, France)

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Tisserand A, Philippi N, Muller C, Durand H, Demuynck C, Loureiro de Sousa P, Ravier A, Sanna L, Botzung A, Mondino M, Blanc F. "I feel therefore I am": interoception as a way to assess the subjective sense of self in dementia with Lewy bodies, an exploratory study. European Journal of Neuroscience, submitted.

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LISTE DES ABREVIATIONS

AI : Autobiographical Interview

CIC : Centre d'Investigation Clinique

CMRR : Centre Mémoire de Ressources et de Recherche

DP : Démence Parkinsonienne

EEG : électroencéphalogramme

FDG : Fluorodeoxyglucose

HTT : tache de détection des battements cardiaques

IRM : Imagerie par résonnance magnétique

LCS : Liquide cérébrospinal

MA : Maladie d'Alzheimer

MCL : Maladie à corps de Lewy

MMSE : Mini-Mental State Examination

MP : Maladie de Parkinson

rTMS : Stimulation magnétique transcrânienne répétitive

SPECT : Tomographie par émission monophotonique

SSS : Sens subjectif de soi

TCSP : Troubles du comportement en sommeil paradoxal

TEP : tomographie par émission de positons

TST : Twenty Statements Test

VBM : Voxel-Based Morphometry

AVANT-PROPOS

Les difficultés à rappeler des évènements du passé constituent fréquemment les premiers symptômes des patients suspects de développer une maladie neuroévolutive cognitive. Usuellement qualifiés de « troubles de la mémoire autobiographique », ces difficultés pourraient découler d'une atteinte plus globale de la conscience de soi, ou « self ». En effet, la mémoire autobiographique est une forme de conscience de soi étendue dans le temps, dont l'atteinte est fréquemment associée à d'autres modifications du self, telles que des changements dans la personnalité, des représentations identitaires qui s'estompent ou encore un manque de conscience à l'égard de ses troubles. Les études sur les substrats neuroanatomiques du self font ressortir les régions de la ligne corticale médiane, à coté desquelles certains travaux suggèrent un rôle pour l'insula. L'insula, ou le « cinquième lobe du cerveau », est une structure cérébrale qui se situe en profondeur des opercules frontales, temporales et pariétales, et qui se trouve parmi les premières régions cérébrales atteintes dans la maladie à corps de Lewy (MCL). La MCL est la deuxième maladie neuroévolutive cognitive, en termes de fréquence, après la maladie d'Alzheimer (MA), et représente environ 20% des troubles neurocognitifs majeurs. La MCL, par ses altérations du self qui semblent évidentes pour les proches et les cliniciens, et par son atteinte insulaire précoce, constitue un modèle d'étude privilégié pour explorer le self. L'objectif général de ce travail est d'étudier le self dans la MCL dès le stade prodromal, avec un intérêt particulier pour le lien entre l'insula et le self. Le self sera étudié à travers un regard comportemental, aux moyens d'outils de neuropsychologie, et ses substrats neuroanatomiques seront explorés par des études en imagerie volumétrique.

LE SELF DANS LA MALADIE À CORPS DE LEWY : PARTIE THÉORIQUE

PARTIE THEORIQUE : LE SELF DANS LA MALADIE À CORPS DE LEWY

1. La maladie à corps de Lewy

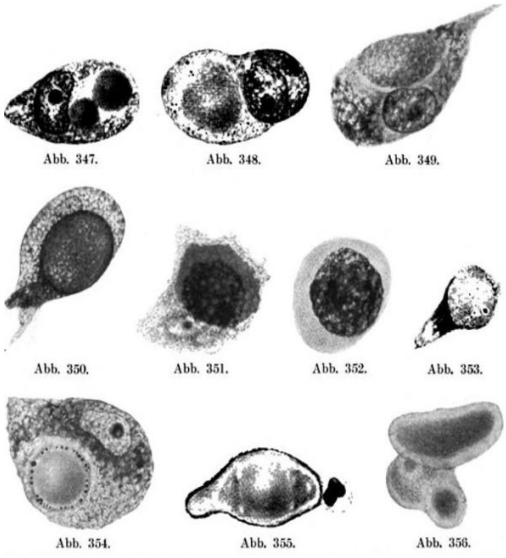

Figure 1 *Dessin de corps de Lewy, issu de l'ouvrage « La théorie du tonus et du mouvement », F.H. Lewy, 1923.*

La MCL est une maladie neuroévolutive appartenant à la famille des synucléinopathies, dont la topographie des lésions affecte à la fois le système nerveux central et le système nerveux périphérique. L'extension des lésions entraine une dégradation progressive et fluctuante du fonctionnement cognitif, moteur et neurovégétatif, qui explique sa présentation polymorphe. Fréquemment considérée comme une entité « hybride » entre les maladies d'Alzheimer et de Parkinson, la MCL partage des lésions anatomiques et histologiques partiellement communes avec les deux maladies, alors qu'elle présente des traits cliniques tout à fait caractéristiques. La MCL serait la deuxième protéinopathie parmi les maladies neuroévolutives en termes de fréquence après la maladie d'Alzheimer, elle reste pourtant aujourd'hui encore, mal connue et largement sous-diagnostiquée (Nelson et al., 2010).

1.1. Contexte historique

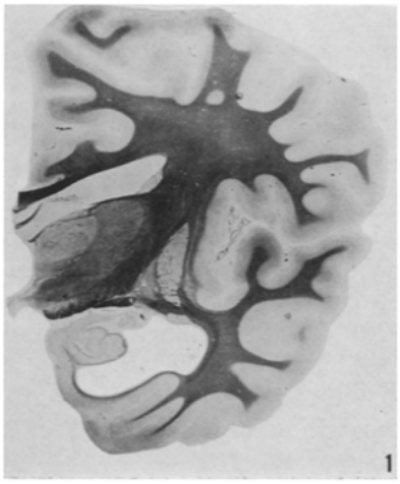

Figure 2 *Coupe histologique montrant l'atrophie cérébrale de la patiente qui a permis la découverte des corps de Lewy corticaux, Kosaka et al., 1976*

Les corps des Lewy (Figure 1) sont décrits pour la première fois en 1912 par le neurologue Berlinois Fritz Heinrich Lewy. Il s'agit d'inclusions neuronales intracytoplasmiques, observées dans le noyau de la substance innominée et dans le noyau dorsal du nerf vague. Cette description fait référence à un patient atteint de « *paralysis agitans* », qui sera connue plus tard sous l'appellation de maladie de Parkinson (MP). Lewy découvrira en 1923 les mêmes corps de Lewy dans la substance noire, chez des patients atteints de MP (Lewy, 1923). Jusque dans les années 1950, les corps de Lewy seront considérés comme un marqueur

histologique spécifique de la MP. C'est en 1952 que les premiers cas de patients présentant des corps de Lewy sans maladie de Parkinson authentique, sont décrits (Beheim-Schwarzbach, 1952). En 1976, le psychiatre Japonais Kenji Kosaka découvre des corps de Lewy corticaux, au cours de l'examen post-mortem du cerveau d'une patiente (Figure 2) ayant présenté un tableau de troubles cognitifs progressifs, associés à des troubles moteurs (Kosaka et al., 1976). Finalement, l'équipe Japonaise propose le « diffuse type of Lewy body disease », (maladie à corps de Lewy diffus) en tant que nouvelle maladie, en 1984 (Kosaka et al., 1984). À l'occasion du premier consortium international organisé à Newcastle en 1995, la pathologie est universellement définie en tant que « dementia with Lewy bodies » (démence à corps de Lewy), et les critères diagnostiques y sont précisés. (McKeith et al., 1996).

1.2. Epidémiologie

La MCL est une maladie neuroévolutive relativement récente, dont la prévalence et l'incidence sont difficiles à estimer, principalement en raison du faible nombre d'études épidémiologiques. Elle est généralement considérée comme la deuxième forme de maladie neuroévolutive la plus courante chez les personnes de plus de 65 ans, certaines études affirment même qu'elle représenterait jusqu'à 30.5% des cas de troubles neurocognitifs majeurs (Stevens et al., 2002). Cependant, il existe une variabilité significative des données sur sa prévalence ; les dernières méta-analyses dédiées à l'étude de ces paramètres suggèrent qu'elle représenterait plutôt 4 à 8% des cas de troubles neurocognitifs majeurs de type neuroévolutifs (Hogan et al., 2016; Vann Jones & O'Brien, 2014; Z. Walker et al., 2015). Son incidence dans la population générale est estimée entre 0.5 et 1.6 cas par 1000 personnes par an (Hogan et al., 2016; Vann Jones & O'Brien, 2014). En termes de sex-ratio, les données sont hétérogènes, mais la plupart des études s'accordent autour d'une légère prédominance du sexe féminin (Vann Jones & O'Brien, 2014). C'est également ce que suggère une étude transversale réalisée à partir des données de la Banque Nationale Alzheimer française, qui incluait 10 309 patients atteints de MCL, dont 54.7% de femme pour 45.3% d'hommes (Mouton et al., 2018). Concernant le pronostic de la MCL, les études longitudinales la comparant à la MA révèlent un taux de mortalité plus élevé, avec un déclin cognitif plus rapide (Mueller et al., 2017). Malgré des critères cliniques qui ont récemment été révisés, et des biomarqueurs validés (McKeith et al., 2017, 2020), la MCL reste largement sous-diagnostiquée

dans les soins cliniques de routine, souvent confondue avec la MA, la MP ou encore avec des pathologies psychiatriques tardives. Elle est néanmoins fréquente et constitue un problème de santé publique actuel et pour l'avenir.

1.3. Physiopathologie

La physiopathologie de la MCL repose essentiellement sur la présence intracellulaire d'alpha-synucléine mal-conformée formant des corps de Lewy ou neurites de Lewy, tel que cela a été décrit lors du premier consortium international dédié à la MCL (McKeith et al., 1996).

1.3.1. Neuropathologie

1.3.1.1. L'α-synucléinopathie

L'α-synucléine est une protéine transmembranaire de 140 acides aminés codés par le gène SNCA sur le chromosome 4 du génome humain. Plusieurs études suggèrent que l'α-synucléine existe en condition physiologique sous différentes formes (Binolfi et al., 2006; Davidson et al., 1998; Uversky, 2007). Ses interactions avec de nombreux autres partenaires rendent difficile la définition de ses fonctions précises (Dehay et al., 2015). Lorsqu'elle est anormalement conformée, l'α-synucléine peut se présenter sous forme de fibrilles riches en feuillets β, qui forment des agrégats insolubles, constituant la base des corps et neurites de Lewy (Uversky, 2007). En dehors de l'α-synucléine agrégée, l'analyse microscopique des corps de Lewy révèle également la présence de neurofilaments et d'ubiquitine (Goldman et al., 1983; Kuzuhara et al., 1988). Deux types de corps de Lewy ont été décrits dans la MCL (Outeiro et al., 2019). Les

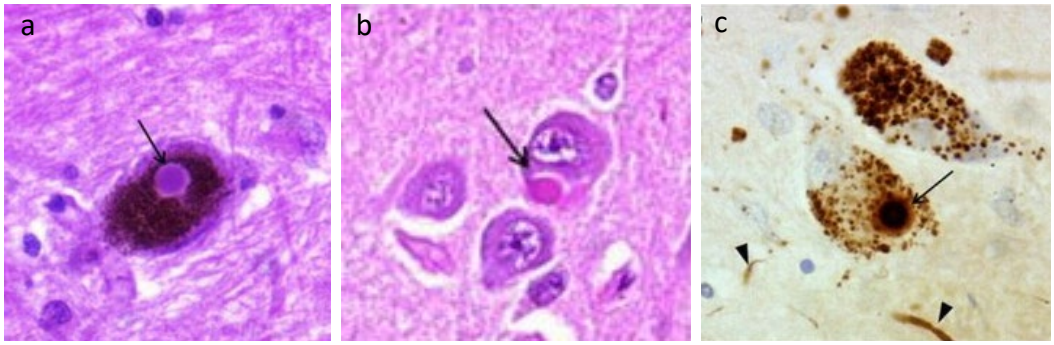

Figure 3 *Corps et neurites de Lewy. a corps de Lewy dans un neurone pigmenté de la substance noire. b corps de Lewy cortical dans l'hippocampe au niveau de CA 1. c corps de Lewy (flèche) et neurite de Lewy (pointes) dans la substance noire. (a, b) éosine hématoxyline; (c) Immunocoloration anticorps anti-α-synucléine.*

corps de Lewy du tronc cérébral sont des inclusions intracytoplasmiques globulaires éosinophiles de 5 à 25 µm de diamètre, possédant un centre homogène très dense entouré d'un halo périphérique, qui se situent plus volontiers dans les neurones dopaminergiques de la substance noire (Duffy & Tennyson, 1965; Lewy, 1923) (figure 3, a.). Les corps de Lewy corticaux qui se situent dans les Vème et VIème couche du néocortex sont également éosinophiles mais leur forme tantôt arrondie, tantôt angulaire est plus irrégulière et ils sont dépourvus d'un halo distinctif (Kosaka et al., 1976; Okazaki et al., 1961) (figure 3, b.). Les neurites de Lewy contiennent quant à eux des filaments similaires à ceux identifiés dans les corps de Lewy, et sont localisés dans les prolongements neuronaux (Dickson et al., 1991) (figure 3, c.).

1.3.1.2. Mécanisme de toxicité de l'α-synucléinopathie

Les mécanismes liants l'accumulation pathologique d'α-synucléine à la perte neuronale sont encore mal compris. Il existe de toute évidence une dégénérescence des neurones dopaminergiques de la substance noire, parallèlement à une perte neuronale plus variable dans d'autres régions du cerveau. Des études soulignent une dissociation entre la concentration élevée en corps de Lewy et une perte neuronale limitée dans de nombreuses régions cérébrales, telles que l'amygdale, le noyau moteur dorsal du nerf vague, le locus coeruleus et le néocortex (Harding et al., 2002; Hoogendijk et al., 1995; Kingsbury et al., 2010; McCann et al., 2016; Pedersen et al., 2005). Le degré d'atrophie dans la MCL est par ailleurs plus modéré que dans la MA, tant au stade prodromal (Blanc et al., 2015, 2016) qu'au stade de troubles neurocognitifs majeurs (Zhong et al., 2014). Ces données suggèrent que l'accumulation pathologique d'α-synucléine conduirait à des dysfonctionnements neuronaux multiples (Wong & Krainc, 2017), en sus de la toxicité menant à la mort cellulaire.

1.3.1.3. Topographie lésionnelle de l'α-synucléinopathie

Bien que partageant des lésions neuropathologiques caractéristiques, la MCL, la MP et la démence Parkinsonienne (DP, i.e. trouble neurocognitif majeur associé à la MP) se distinguent par l'enchainement chronologique des symptômes cliniques, à l'image de la propagation des lésions. Le modèle de Braak et Braak rend compte d'une propagation caudo-rostrale de la pathologie de l'α-synucléine selon six stades, avec une atteinte allant du tronc cérébral vers

les ganglions de la base, puis s'étendant secondairement au néocortex (Braak et al., 2003). Dans la MP, la propagation agrégative de l'α-synucléine se limite au tronc cérébral et aux régions limbiques (Stade 1-3 selon Braak) et est à l'origine des symptômes moteurs, alors qu'elle s'étend progressivement au néocortex dans la DP (Stade 4-6 selon Braak) et est à l'origine de l'émergence des symptômes cognitifs. Ce schéma de propagation n'est pas applicable à la MCL pour laquelle il existe une plus grande variabilité dans la topographie des lésions. Dans la plupart des cas de MCL, les régions affectées initialement sont le système limbique et le néocortex. Il peut toutefois exister une prédominance de l'atteinte dans le tronc cérébral, et plus rarement dans l'amygdale ou limitée au bulbe olfactif (I. G. McKeith et al., 1996, 2017; The Arizona Parkinson's Disease Consortium et al., 2009). Ainsi il existe un large spectre de signes et symptômes dès le stade prodromal, bien que la MCL demeure dominée par les troubles cognitifs qui sont plus saillants que les manifestations extrapyramidales (McKeith et al., 2017; Outeiro et al., 2019). Au cours de la maladie, l'α-synucléine se propage à l'ensemble du cerveau, se transmettant de cellule en cellule, de la même manière que la protéine prion pathologique (Brundin et al., 2008; Li et al., 2008). Des dépôts d'α-synucléine ont également été détectés dans les systèmes nerveux autonomes périphériques de patients atteints de synucléinopathies, tel que dans le cœur ou le système gastro-intestinal (Beach et al., 2021; Braak et al., 2006; Javanshiri et al., 2022; Wakabayashi et al., 1988).

1.3.1.4. Autres protéinopathies

Outre la présence des corps de Lewy, la MCL partage des lésions histologiques communes avec la MA, y compris dans sa forme pure. Environ 50% des patients atteints de MCL présentent également une augmentation des dépots de protéine β-amyloïde, au stade de troubles neurocognitifs majeurs (Jellinger, 2009; McKeith et al., 2017; Petrou et al., 2015). Ce constat est moins évident dans la MCL au stade prodromal, durant lequel les valeurs d'Aβ42 dans le liquide cérébrospinal (LCS) sont normales dans la plupart des cas, ou ne montrent qu'une discrète diminution (Bousiges et al., 2018). Des études ont montré qu'il existe également des dépots anormaux de protéine β-amyloïde dans la DP bien que la charge amyloïde soit moins importante que dans la MCL (Ballard et al., 2006; L. Walker et al., 2015). La relation qu'entretiennent la β-amyloïde et l'α-synucléine est mal connue. Néanmoins, une étude suggère qu'il existe une relation synergique entre les deux protéines, puisque les taux

d'Aβ42 semblent positivement corrélés à l'α-synucléine phosphorylée en sérine 129, dans la plupart des régions cérébrales (Swirski et al., 2014). Les plaques amyloïdes observées dans la MCL sont de répartition semblable à celles observées dans la MA (Gomperts et al., 2008; Rowe et al., 2007).

La présence d'inclusions tauopathiques et de dégénérescences neurofibrillaires peuvent être observées chez des patients atteints de MCL, elles définissent alors, conjointement à l'amyloïdopathie, la cooccurence de la MA chez ces patients (Braak & Braak, 1991). La MA étant considérée comme la pathologie la plus fréquemment associée à la MCL (Jellinger, 2009), la présence de ces anomalies histologiques n'est donc pas rare chez les patients atteints de MCL.

1.3.2. Facteurs de risques génétiques et environnementaux

De manière semblable aux autres maladies neuroévolutives, et du fait de sa récente découverte, les causes de la MCL demeurent mal connues.

1.3.2.1. Facteurs génétiques

L'existence d'une composante génétique dans la MCL semble incontestable, puisque l'apparition de la pathologie semble plus probable chez des individus ayant des antécédents familiaux de MP, ou plus généralement de troubles neurocognitifs majeurs (Boot et al., 2013). Par ailleurs, de rares cas familiaux présentant des phénotypes de MP ou de MCL, liés à une duplication ou triplication du gène codant pour l'α-synucléine (SNCA) ont été identifiés (Fuchs et al., 2007; Ikeuchi et al., 2008; Morfis & Cordato, 2006; Obi et al., 2008; Singleton et al., 2002; Zarranz et al., 2004). Il existerait également plusieurs génotypes à risque de développer une MCL (Bras et al., 2014, 2014; Guerreiro et al., 2018; Singleton et al., 2002). Il s'agit par exemple de polymorphismes sur les gènes de l'apolipoprotéine E (ApoE) qui constitueraient un facteur de risque génétique de MCL (Tsuang et al., 2013), en particulier lorsqu'il existe une MA associée (Bousiges et al., 2023). Par ailleurs, des mutations des gènes codant pour la glucocérébrosidase (GBA) représenteraient également un facteur de risque génétique de développer une MCL (Gaubert et al., 2022; Nalls et al., 2013). Outre l'implication de ces 3 gènes, une étude d'association pangénomique (GWAS) a plus récemment identifié d'autres mutations dans les gènes BIN1 et TMEM175 (Chia et al., 2021). Bien que la MCL semble

partager certaines de ces mutations génétiques avec la MA et MP (Bras et al., 2014; Chia et al., 2021; Guerreiro et al., 2018), les données de la littérature semblent plutôt lui attribuer un profil génétique unique, avec une prédisposition génétique qui s'élèverait à 36% (Guerreiro et al., 2018).

1.3.2.2. Facteurs de risques non génétiques

À côté de la composante génétique, des facteurs de risques liés aux antécédents neuropsychiatriques sont également décrits. Dans l'étude cas témoins de Boot et collaborateurs (Boot et al., 2013), l'apparition d'une MCL était plus fréquente chez des individus présentant des antécédents d'anxiété (x7,2), de dépression (x6) ou encore d'accidents vasculaires cérébraux (x2,8). Il semble également exister des facteurs de risques modifiables, qui s'appliquent plus généralement aux maladies neuroévolutives cognitives plutôt qu'à la MCL spécifiquement, parmi lesquels figurent un faible niveau socio-éducatif, la perte d'audition, les traumatismes crâniens, la consommation ethylotabagique, l'isolement social, l'inactivité physique ou encore l'exposition à certains polluants (Livingston et al., 2020).

1.4. Caractéristiques cliniques et biomarqueurs

La MCL est une maladie relativement récente, d'allure polymorphe et d'évolution variable. Elle est considérée comme une entité intégrant un spectre de manifestations cliniques, aux côtés de la DP (Lippa et al., 2007), toutes deux caractérisées par des signes extrapyramidaux associés à un trouble neurocognitif majeur, mais d'apparition chronologiquement différente. La relation nosologique entre la MCL et la DP se précise en 1996, lorsque sont proposés pour la première fois des critères diagnostiques par l' équipe de Newcastle-upon-Tyne, lors d'un consortium international (McKeith et al., 1996). Ces critères sont révisés en 2005, avec l'incorporation de biomarqueurs visant à préciser le diagnostic (McKeith et al., 2005) et l'apparition d'un principe fondamental permettant de distinguer la MCL et la DP, appelé « the one-year rule », qui requière que le trouble cognitif s'installe au plus tard un an après l'apparition des signes extra-pyramidaux dans la MCL (McKeith et al., 2005). Une nouvelle révision précisant davantage la sémiologie et impliquant de nouveaux éléments cliniques parait en 2017 (McKeith et al., 2017). Enfin, en 2020 sont proposés des critères de recherche

pour le diagnostic de MCL au stade prodromal (McKeith et al., 2020), permettant d'identifier des manifestations cliniques inaugurales de cette pathologie.

1.4.1. Critères diagnostiques

Historiquement, les critères diagnostiques ont été subdivisés en critères cardinaux et critères suggestifs, qui permettent d'établir une probabilité du diagnostic de MCL, allant de possible à probable. Le diagnostic de la maladie est dit probable lorsqu'il remplit les critères définis par le rapport du 4ème consensus international pour le diagnostic et la prise en charge, établi lors du consortium international sur la MCL (McKeith et al., 2017). Il s'agit d'un trouble neurocognitif majeur (selon la définition du DSM-5 (American Psychiatric Association & American Psychiatric Association, 2013)), associé à (i) deux critères principaux au minimum, avec ou sans la présence d'un biomarqueur indicatif, ou (ii) un critère principal et un biomarqueur indicatif au minimum. Le diagnostic de la maladie est dit possible en la présence d'un trouble neurocognitif majeur, associé à (iii) un critère principal, sans biomarqueur indicatif, ou (iv) un biomarqueur indicatif au minimum, sans critère principal. Les critères cliniques de diagnostiques de la MCL sont présentés dans le tableau 1, avec les différentes caractéristiques cliniques résumées ci-après. Les critères de MCL au stade prodromal y sont semblables, en dehors de la sévérité du trouble cognitif qui peut être léger, c'est-à-dire n'ayant pas de retentissement sur les activités de la vie quotidienne (Mckeith et al., 2017, 2020).

Tableau 1 *Critères révisés pour le diagnostic de MCL au stade de trouble neurocognitif majeur (McKeith, 2017) ou prodromal (McKeith et al., 2020)*

CRITERES REVISES POUR LE DIAGNOSTIC CLINIQUE DE LA MCL		
TROUBLE NEUROCOGNITIF MAJEUR OU MINEUR (ESSENTIEL)		
Déclin cognitif progressif ; des troubles attentionnels et exécutifs, et visuospatiaux peuvent être présents, sans qu'il n'y ait forcément d'atteinte mnésique aux stades initiaux.		
Probable MCL – Deux critères principaux ou plus, avec ou sans la présence d'un biomarqueur indicatif, OU un critère principal et un ou plusieurs biomarqueurs indicatifs **Possible MCL –** Un critère principal sans biomarqueur indicatif, OU un ou plusieurs biomarqueurs indicatifs, sans critère principal		
CRITERES CLINIQUES CARDINAUX		
- Fluctuations cognitives - Hallucinations visuelles récurrentes - Troubles du comportement en sommeil paradoxal - Syndrome parkinsonien (présence d'au minimum un des trois signes extrapyramidaux : bradykinésie, rigidité, tremblement de repos)		
CRITERES CLINIQUES SUGGESTIFS		
- Sensibilité sévère aux neuroleptiques ; - Instabilité posturale ; - Chutes répétées ; - Syncopes et absences de réaction passagères ; - Hypersomnie ;	- Hyposmie ; - Dysfonction autonomique sévère (e.g. constipation, hypotension orthostatique, incontinence urinaire) ;	- Hallucinations dans d'autres modalités ; - Délires systématisés ; - Apathie ; - Anxiété ; - Dépression
BIOMARQUEURS INDICATIFS		
- Réduction de capture du transporteur de la dopamine dans les noyaux gris centraux, démontré par SPECT (DAT-scan) ou TEP (Fluoro-Dopa) - Diminution de la recapture de la ^{123}iodine-MIBG en scintigraphie myocardique - Confirmation de TCSP par polysomnographie		
BIOMARQUEURS SUGGESTIFS		
- Préservation relative des structures temporales médiales en tomodensitométrie ou à l'IRM - Hypoperfusion ou hypométabolisme des régions occipitales en TEP ou SPECT, +/- signe de l'île cingulaire en TEP au FDG - Activité électrophysiologique postérieure à ondes lentes en EEG, associée à des fluctuations périodiques des bandes de fréquences pré-alpha/thêta		

1.4.1.1. Critères cliniques

La MCL est une affection reposant principalement sur un faisceau d'arguments cliniques, associant troubles cognitifs, psycho-comportementaux, et autres troubles du système nerveux périphérique. La condition sine qua non pour poser le diagnostic de MCL est la présence d'un trouble neurocognitif, soit majeur au stade de démence, soit léger au stade prodromal.

1.4.1.1.1. Critère essentiel

Le trouble neurocognitif majeur fait référence à un déclin cognitif progressif impactant l'autonomie dans les activités instrumentales de la vie quotidienne et interférant avec les activités sociales et professionnelles (American Psychiatric Association & American Psychiatric Association, 2013). Sur le plan neuropsychologique, la MCL se caractérise typiquement par un syndrome sous-cortico-frontal, pouvant être associé à un syndrome postérieur. Il s'agit au premier plan de troubles des fonctions exécutives et attentionnelles (Calderon, 2001), telles qu'évaluées à l'aide de tâches mesurant les capacités de planification (e.g. Figure de Rey (Rey, 1941) ; tour de Londres (Shallice, 1982)), d'initiation verbale (e.g. fluences verbales (Thurstone & Thurstone, 1964)), de flexibilité mentale (e.g. Trail-making-test B, (Goul & Brown, 1970)), de mémoire de travail (e.g. empans de la WAIS (Wechsler, 1997)) ou encore d'attention divisée (e.g. TAP (Zimmerman & Fimm, 2007)). Il existe généralement un ralentissement idéatoire pouvant être évalué à l'aide de tâches mesurant le temps de réaction (e.g. TAP (Zimmerman & Fimm, 2007)) ou la vitesse de traitement de l'information (e.g. Trail-making-test A, (Goul & Brown, 1970), Codes (Wechsler, 1997)). Les déficits susmentionnés peuvent être à l'origine d'un trouble de l'encodage des informations en mémoire antérograde verbale et en mémoire de reconnaissance visuelle (e.g. RLRI16 (Grober et al., 1988); DMS48 (Barbeau et al., 2004)), et d'un trouble des capacités de récupération en mémoire antérograde verbale (e.g. RLRI16 (Grober et al., 1988)), secondaire à un déficit de mise en place de stratégies de récupération (Querry et al., 2023). Des troubles neurovisuels, notamment visuo-spatiaux et visuo-constructifs peuvent être associés au profil cognitif, voire inaugurer les troubles cognitifs (Collerton et al., 2003; McKeith et al., 2017), et sont classiquement évalués par des tâches de détection d'objets ou de reproduction de figures complexes (e.g. figure complexe de Rey (Rey, 1941) ; VOSP (Schmidt et al., 1999)). Enfin, l'une des particularités du profil cognitif des

patients atteints de MCL est qu'il est marqué par de franches fluctuations cognitives, avec des variations importantes de l'attention et de l'état de vigilance (McKeith et al., 1996) (cf. § 1.4.1.1.2.). De façon moins fréquente, il est possible d'observer un syndrome d'amnésie hippocampique associé (Kemp et al., 2017; Querry et al., 2023), qui se caractérise par un trouble du stockage des informations en mémoire, indépendamment du fonctionnement de l'encodage. Les troubles cognitifs sont présents dès le stade prodromal, le plus souvent caractérisés par des troubles de la mémoire de reconnaissance visuelle, de mémoire court terme et de travail, de flexibilité mentale, associés à un ralentissement de la vitesse de traitement de l'information (Kemp et al., 2017; Wyman-Chick et al., 2022).

1.4.1.1.2. Critères cliniques cardinaux

Les **fluctuations cognitives** incarnent un critère diagnostique clé de la pathologie. Il s'agit d'altérations spontanées et transitoires du fonctionnement cognitif, souvent accompagnées de variations prononcées de l'attention et de l'état de vigilance. Elles sont présentes chez 80 à 90 % des patients atteints de MCL au stade de troubles neurocognitifs majeurs (McKeith et al., 1996, 2017), et environ 40% des patients au stade prodromal (Blanc et al., 2022; Wyman-Chick et al., 2022). Ces fluctuations cognitives se traduisent par des incohérences dans le comportement, le discours, une labilité des capacités attentionnelles, d'orientation, ou encore une fixité du regard traduisant une altération de l'état de conscience. La fréquence et la durée de ces épisodes sont variables d'un patient à l'autre, pouvant s'étaler entre une minute et un mois (McKeith et al., 1996). Elles peuvent être dépistées dans la pratique clinique lors de l'interrogatoire avec l'aidant, avec des échelles telles que *l'échelle d'évaluation clinique des fluctuations* (M. P. Walker et al., 2000), *l'échelle semi-structurée d'évaluation des fluctuations au cours d'une journée* (M. P. Walker et al., 2000) ou encore *l'échelle composite de la Mayo clinic* (Ferman et al., 2004). Ces questionnaires semi-structurés permettent d'évaluer différentes sphères (c.-à-d. somnolence diurne, état léthargique, regard dans le vide, discours épisodiquement désorganisé), en mesurant la gravité et la fréquence des fluctuations. Des logiciels d'évaluation neuropsychologique tels que la TAP (Zimmerman & Fimm, 2007) permettent également d'objectiver les fluctuations cognitives, par l'enregistrement des variations du niveau attentionnel dans le temps.

Les **hallucinations visuelles** sont le plus souvent complexes, récidivantes, persistantes et très caractéristiques de la présence de corps de Lewy. Elles concernent près de 80% des patients au stade de troubles neurocognitifs majeurs (McKeith et al., 2017). Il s'agit habituellement d'hallucinations complexes, mettant en scène des personnages inconnus ou familiers, des animaux ou des objets. Elles sont parfois accompagnées de sensations de passage, de présence, ou encore d'illusions visuelles. Leur apparition prédomine généralement en fin de journée ou durant la nuit, elles sont le plus souvent analysées et critiquées par le patient. Les hallucinations visuelles peuvent être précoces, voire inaugurales, et peuvent constituer un des modes d'entrée psychiatrique de la MCL (McKeith et al., 2020). Dans la pratique clinique, les hallucinations peuvent être détectées et qualifiées à l'aide de questionnaires tels que l'échelle multimodale d'hallucinations psycho-sensorielles (De Chazeron et al., 2015), ou le questionnaire de Fénelon (Fénelon et al., 2010).

Le **syndrome parkinsonien** est défini dans la MP par la présence d'une bradykinésie, associée à un tremblement de repos, une rigidité musculaire, ou les deux (Postuma et al., 2015), volontiers asymétrique. Dans la MCL, un seul de ces trois items cardinaux est nécessaire pour affirmer la présence d'un syndrome parkinsonien, le tremblement de repos étant moins fréquent que la présence des deux autres symptômes (McKeith et al., 2005). Le syndrome parkinsonien est présent dans 85% des cas de patients au stade de troubles neurocognitifs majeurs (McKeith et al., 2017), et jusqu'à 70% des patients au stade prodromal (Wyman-Chick et al., 2022). Le principal outil de diagnostic du syndrome parkinsonien reste l'échelle d'évaluation unifiée de la maladie de Parkinson (UPDRS) (Fahn, S. & Elton, R.L., 1987).

Les **troubles du comportement en sommeil paradoxal** (TCSP) qui faisaient précédemment parti des critères suggestifs, deviennent l'un des critères cardinaux dans la révision de 2017 (McKeith et al., 2017). Ils peuvent apparaitre plusieurs décennies avant les troubles cognitifs ou les troubles moteurs, et sont considérés comme un signe précurseur du développement d'une α-synucléinopathie (Postuma et al., 2019). Ils sont présents dès le stade prodromal chez plus de 50% des patients (Wyman-Chick et al., 2022), et jusqu'à 76% des patients au stade de troubles neurocognitifs majeurs (Ferman et al., 2011). Les TCSP se caractérisent par une activité onirique intense associée à une levée de l'atonie musculaire. Les rêves et cauchemars,

souvent récurrents, sont accompagnés d'agitations des membres, de déambulation, de vocalisation ou encore de violences verbales qui imitent le rêve. Ils sont souvent décrits à l'interrogatoire comme des « rêves éveillés ». Ils peuvent être dépistés dans la pratique clinique par des échelles interrogeant le patient et son partenaire, telles que l'échelle de sommeil de la Mayo clinic (B. F. Boeve et al., 2011), ou par une polysomnographie.

1.4.1.1.3. Critères cliniques suggestifs

Bien que manquants de spécificité, les critères suggestifs regroupent des symptômes fréquents suggérant la présence d'une MCL, en particulier s'ils persistent dans le temps ou s'ils surviennent en « *clusters* » (Matar et al., 2020; McKeith et al., 2017). Ces symptômes peuvent se caractériser par des troubles dysautonomiques sévères, tels que de l'hypotension orthostatique, la constipation ou l'incontinence urinaire, mais également d'instabilités posturales ou de chutes répétées. Les critères suggestifs incluent également des troubles psycho-comportementaux tels que la présence d'hallucinations dans d'autres modalités (e.g. auditives, cénesthésiques), d'épisodes de délire, d'une apathie, d'une anxiété et de dépression. Il peut également exister une hypersensibilité aux neuroleptiques, une hypersomnie ou une hyposmie.

1.4.1.2. Marqueurs biologiques

Il n'existe pas, dans la pratique clinique, de biomarqueurs *in vivo* permettant d'identifier une pathologie à corps de Lewy, bien que de nouveaux outils soient à l'étude (cf. § 1.4.1.2.3.). En revanche, plusieurs biomarqueurs indirects accompagnent le diagnostic clinique.

1.4.1.2.1. Biomarqueurs indicatifs

Le **DaTSCAN** représente l'examen d'imagerie nucléaire le plus utilisé pour évaluer l'intégrité du système dopaminergique nigrostriatal. Il permet, à l'aide d'un radiotraceur au ioflupane, d'identifier en tomographie par émission monophotonique (SPECT), une diminution de la fixation du transporteur de la dopamine (DAT) dans le striatum, indiquant une dénervation présynaptique des voies dopaminergiques (McKeith et al., 2005). Le DaTSCAN présente une sensibilité correcte (78%) et une haute spécificité (90%) au stade de troubles cognitifs majeurs (McKeith et al., 2007), et constitue un examen d'intérêt pour discriminer une MCL d'une

maladie d'Alzheimer (figure 4), par exemple chez un patient ne présentant pas de syndrome parkinsonien. Il présente de moindre performances diagnostiques dans les cas de suspicion de MCL prodromique, ou il montre une faible sensibilité de 54%, avec une spécificité toujours élevée à 89% (Thomas et al., 2019).

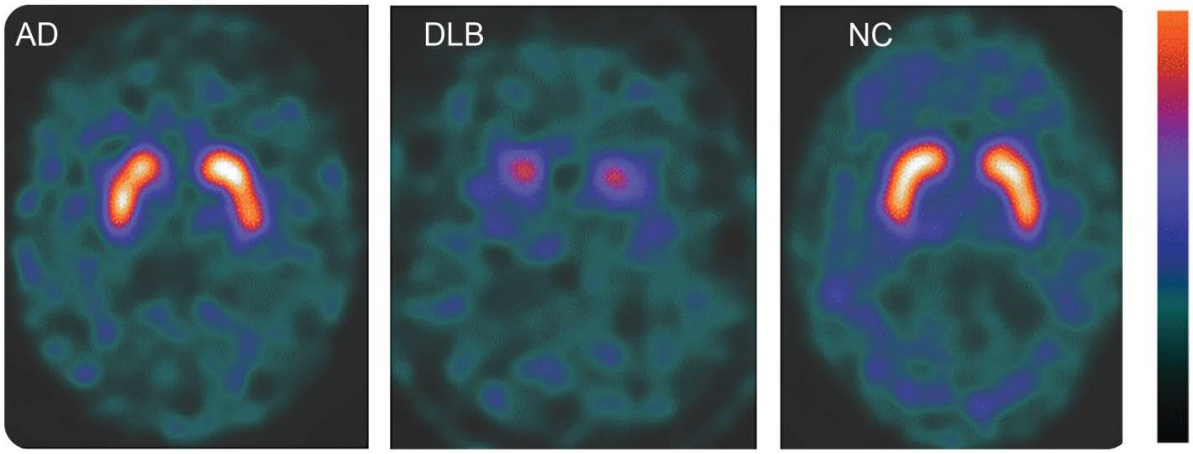

Figure 4 *Scintigraphie au DaTSCAN montrant une diminution de la fixation du transporteur de la dopamine dans le striatum, chez des patients atteints de maladie à corps de Lewy (DLB), de maladie d'Alzheimer (AD) et des sujets contrôles sains (NC)*

La **scintigraphie myocardique au MetaIodoBenzylGuanidine** (MIBG) est une autre technique d'imagerie évaluant l'intégrité de l'innervation sympathique cardiaque postganglionnaire. Elle permet de mettre en évidence une diminution de la fixation d'un radiotraceur analogue de la guanéthidine, indiquant des lésions du nerf sympathique du myocarde (Hanyu et al., 2006; McKeith et al., 2017), à l'origine de dysfonctionnement autonomiques. De la même façon que le DaTSCAN, la scintigraphie myocardique est moins intéressante dans un contexte de MCL prodromique, puisque sa sensibilité est de 46% (Roberts et al., 2021).

La **polysomnographie** permet de mettre en évidence une perte de l'atonie musculaire et une activité motrice excessive durant le sommeil paradoxal (cf. § 1.4.1.1.2.). La confirmation des TCSP par polysomnographie chez des patients avec troubles neurocognitifs majeurs permet d'estimer à plus de 90% la probabilité d'occurrence d'une synucléinopathie (B. F. Boeve et al., 2013). La mise en évidence de TCSP par polysomnographie chez des patients avec troubles neurocognitifs légers indique également une forte probabilité de synucléinopathie prodromique sous-jacente (McKeith et al., 2020).

1.4.1.2.2. Biomarqueurs suggestifs

Les biomarqueurs suggestifs apportent un soutien au diagnostic de MCL, bien que ne relevant pas d'une authentique spécificité.

En **imagerie anatomique**, il existe une relative préservation des structures temporales mésiales. Bien que ne figurant pas dans les critères diagnostiques officiels, une autre particularité morphométrique de la MCL est l'atrophie insulaire bilatérale (Burton et al., 2002; Whitwell et al., 2007), qui est visible dès le stade prodromal (figure 5) (Blanc et al., 2015; Roquet et al., 2017). L'atteinte est homogène sur l'ensemble de l'insula, et concerne à la fois sa partie antérieure et postérieure, qui sont toutes deux impliquées dans de nombreux processus cognitifs, émotionnels, somatosensoriels (cf. § 2.).

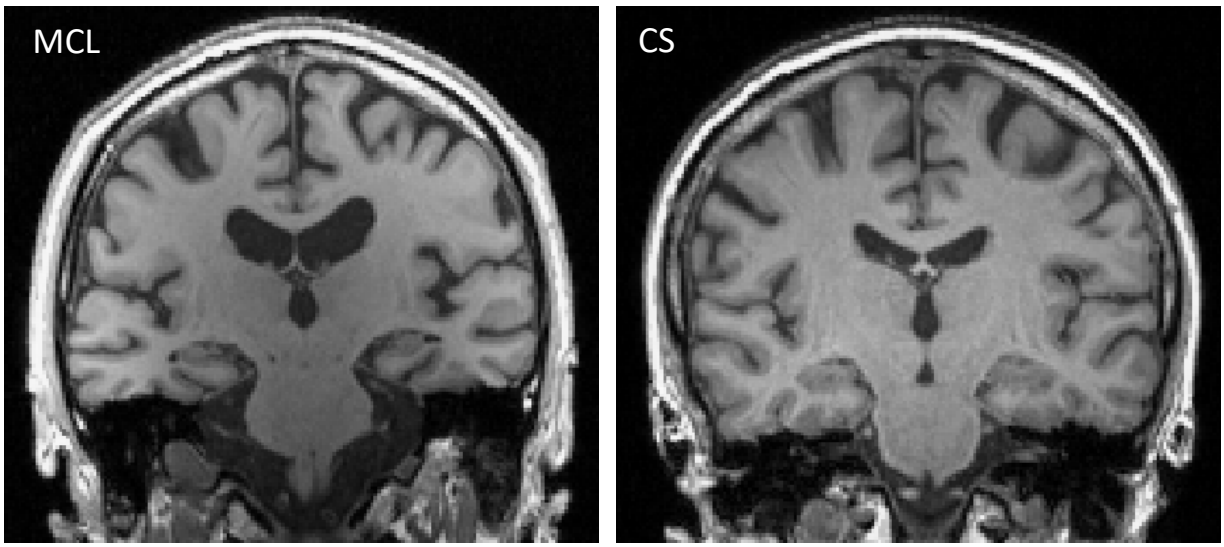

Figure 5 *IRM cérébrale montrant une atrophie insulaire plus marquée chez les patients atteints de maladie à corps de Lewy, comparativement aux sujets contrôles sains (CS).*

En **imagerie nucléaire**, on peut observer une hypoperfusion en SPECT/ un hypométabolisme en tomographie par émission de positons (TEP) au fluorodeoxyglucose (FDG), des régions occipitales, épargnant le cortex cingulaire postérieur (signe de l'île cingulaire).

En **électrophysiologie**, il peut exister une activité postérieure à ondes lentes objectivée par l'électroencéphalogramme (EEG), montrant des fluctuations périodiques des bandes de fréquences pré-alpha/thêta (McKeith et al., 2017).

1.4.1.2.3. Autres biomarqueurs

Parmi les autres biomarqueurs, il existe fréquemment une diminution de l'Aβ42 dans le LCS (Bousiges et al., 2018) associée à une augmentation des dépôts de protéine β-amyloïde dans le cerveau visible en TEP amyloïde, chez plus de 50% des patients atteints de MCL au stade de trouble neurocognitif majeur, (Ossenkoppele et al., 2015). Cette diminution est moins évidente au stade prodromal, durant lequel les patients ne présentent que peu, ou pas, de diminution d'Aβ42 dans le LCS (Bousiges et al., 2018).

Les recherches actuelles se concentrent sur l'identification de biomarqueurs spécifiques des synucléinopathies, tels que le développement de traceurs TEP spécifiques de l'α-synucléine (Korat et al., 2021) ou l'évaluation de la concentration d'α-synucléine dans le LCS (Lilamand et al., 2022). Une autre technique innovante qui suscite l'intérêt des chercheurs est la « RT-QuIC » (real-time quaking-induced conversion) qui permet d'identifier la présence d'α-synucléine pathologique sur la base de l'effet « prion-like » de l'α-synucléine (Blanc & Bousiges, 2022; Bousiges & Blanc, 2022; Hall et al., 2022).

1.4.1.3. Évolution de la maladie

Les corps de Lewy peuvent être présents dans le système nerveux plusieurs années avant que le diagnostic clinique ne soit évoqué (Savica et al., 2010, 2018). Les symptômes, qui s'installent insidieusement, présentent par ailleurs une grande hétérogénéité, balayant différents domaines qui peuvent être cognitifs ou non cognitifs. Le consortium international sur la MCL a proposé de distinguer trois phénotypes cliniques de MCL prodromique (McKeith et al., 2016). Dans le premier prédomine un trouble neurocognitif léger, concernant une ou plusieurs sphères cognitives, plus généralement défini par des troubles attentionnels et exécutifs, pouvant être associés à des troubles neurovisuels, avec une préservation relative des fonctions mnésiques et langagières (Ferman et al., 2006). Le deuxième phénotype est défini par l'apparition d'états confusionnels aigus spontanés ou induits, sans qu'il n'y ait nécessairement de troubles cognitifs (Gore et al., 2015). Le troisième est caractérisé par une prédominance des symptômes psychiatriques (Birkett et al., 1992; Kosaka, 1990), il s'agit généralement de l'apparition d'un épisode dépressif majeur, survenant en moyenne 8 ans avant le diagnostic de MCL (Gunawardana et al., 2023), et pouvant être associé à des hallucinations visuelles ou dans une autre modalité, ou à des délires systématisés tels qu'un

syndrome de Capgras. Ces trois phénotypes cliniques ne sont pas systématiques et peuvent se chevaucher. Il n'est pas exclu que d'autres manifestations cliniques puissent inaugurer la maladie, comme par exemple les TCSP qui peuvent apparaitre plusieurs décennies avant le stade de trouble neurocognitif majeur (Claassen et al., 2010), ou bien les troubles neurovégétatifs (Blanc et al., 2022). L'évolution se fait vers une aggravation progressive, en particulier lorsqu'il existe un syndrome parkinsonien évident dès le début de la maladie (Aveneau et al., 2023) ou une MA associée (Blanc et al., 2017). La MCL couvre un large spectre de symptômes qui peuvent être cognitifs, neuropsychiatriques, dysautonomiques, moteurs (Cognat et al., 2023; McKeith et al., 2017, 2020; Postuma et al., 2013; Z. Walker et al., 2015; Wyman-Chick et al., 2022), et que les patients peuvent, ou peuvent ne pas développer durant la progression de la maladie (McKeith et al., 1996). L'espérance de vie est difficile à évaluer puisque le diagnostic, qui repose principalement sur des critères cliniques, est généralement tardif. On estime néanmoins le pronostic vital entre 1,9 à 6,3 ans après le diagnostic, quand le diagnostic est porté à un stade de troubles neurocognitifs majeurs, indiquant une plus grande fragilité de ces patients par rapport à ceux atteints de MA (Mueller et al., 2017). À l'inverse, l'évolution apparait plus lente que dans la MA au stade prodromal (Blanc et al., soumis).

1.4.1.4. Prise en charge et perspectives thérapeutiques

Bien que la recherche thérapeutique dans les maladies neuroévolutives soit très active, il n'existe actuellement pas de traitement étiologique de la MCL. Les principales voies de recherche thérapeutiques explorées sont les traitements « *disease-modifyier* » dont l'objectif est de modifier le cours évolutif de la maladie (Palermo et al., 2018; Velayudhan et al., 2017), les immunothérapies et les polythérapies, qui pourraient être proposées à un stage plus avancé de la maladie (Bergström et al., 2016; Schneeberger et al., 2016; Valera & Masliah, 2016).

Aujourd'hui, les patients peuvent bénéficier de traitements pharmacologiques permettant de soulager les symptômes, comme la Rivastigmine et le Donepezil (c.-à-d. anticholinerstérasiques), dont l'efficacité a été démontrée, et qui permettent une amélioration significative des symptômes psychocomportementaux tels que l'apathie, les hallucinations, l'anxiété, et du fonctionnement cognitif (McKeith et al., 2000). Les symptômes neuropsychiatriques de type hallucinations et délires peuvent également être traités par

Clozapine, et depuis peu par Pimavansérine dont l'efficacité a récemment été montrée (Hawkins & Berman, 2017). Dans les cas complexes et sévères de la MCL associant délire et syndrome frontal, l'association de la Pimavansérine avec la Trazodone pourrait être utile (Muller et al., 2023). Les autres neuroleptiques sont contre-indiqués dans la MCL. Concernant la prise en charge des symptômes extrapyramidaux, l'administration de Lévodopa est généralement efficace et bien tolérée chez les patients atteints de MCL, néanmoins, un tiers des patients peuvent présenter une majoration des hallucinations, agitations ou de la somnolence (Molloy, 2005). Enfin, l'administration de Mélatonine permet de réduire la sévérité et la fréquence des TCSP (B. Boeve, 2003). Dans certains cas, les patients qui présentent des TCSP très sévères avec des comportements agressifs peuvent se voir proposer du Clonazépam à faibles doses (0.5-1.0 mg).

D'autres modes de prise en charge non pharmacologique concernent la kinésithérapie pour lutter contre l'hypertonie et les troubles posturaux, la neuropsychologie et l'orthophonie qui proposent des séances de psychoéducation et de remédiation cognitive. Par ailleurs, d'autres pistes telles que les thérapies de pleine conscience « m*indfulness-based cognitive therapy* » ou encore la stimulation magnétique transcrânienne répétitive (rTMS) méritent d'être explorées.

CONCLUSION PARTIE 1 : La MCL est une pathologie neuroévolutive invalidante au pronostic relativement sombre. Encore trop souvent sous-diagnostiquée, elle ne bénéficie, à l'heure actuelle, d'aucune solution thérapeutique curative. Le développement de marqueurs biologiques spécifiques est au cœur des recherches actuelles, toutefois son diagnostic repose essentiellement sur un faisceau d'arguments cliniques. A l'image des autres maladies neuroévolutives, les troubles cognitifs qui rythment la progression de la MCL sont souvent accompagnés de modifications comportementales. Les proches des patients confient fréquemment ne plus les reconnaître, comme s'ils présentaient une altération identitaire. Ces changements cognitifs et comportementaux peuvent échapper à la conscience des patients par les mécanismes de l'anosognosie, dont les connaissances dans la MCL sont lacunaires (Calil et al., 2021). Ces modifications pourraient être en lien avec une atteinte diffuse du « soi » ou « self », s'étendant des aspects les plus élémentaires tels que l'intéroception, aux aspects les plus élaborés tels que les souvenirs autobiographiques. Or, l'une des structures qui semble jouer un rôle clé dans les réseaux cérébraux du self, notamment dans ses aspects élémentaires, est l'insula, qui est précocement atteinte dans la MCL. En supposant que les aspects primitifs du self servent de fondations aux aspects les plus élaborés, l'atteinte de l'insula pourrait mener à un effondrement global du self dans la MCL. Ainsi, à travers son atteinte insulaire précoce, la MCL incarne un modèle d'étude privilégié dans l'exploration du self.

2. Self & insula

Le concept de l'identité, qui appartient à la question du self, fait l'objet d'interrogations depuis l'antiquité, et certains philosophes historiques tels que Platon, Descartes, Locke ou encore Hume ont déjà tenté d'y répondre. À partir du XIX^{ème} , les psychologues et autres intervenants de la communauté scientifique s'intéressent à la question de manière plus approfondie (James, 1890). Il s'agit au sens large, du sentiment de soi, du sens de soi, de la conscience de soi, de l'identité personnelle, de ce qui nous caractérise, et de ce que nous ressentons, pensons, faisons en tant qu'individu unique, mais également de ce que nous avons vécu et de ce que nous projetons de vivre. Dans le discours commun, le terme « soi » fait référence au sentiment que quelque chose « est à mon propos, me concerne ». Il existe différentes nomenclatures selon les auteurs ; néanmoins, le self est presque systématiquement défini à la fois en tant que sujet (« je ») et en tant qu'objet (« moi ») (Conway, 2005; Conway & Pleydell-Pearce, 2000; Damasio, 2003; Gallagher, 2000; James, 1890; Neisser, 1988; Prebble et al., 2013), et à travers un spectre temporel, avec la notion de self au moment présent et de continuité dans le temps. Dans ce manuscrit, nous nous referrerons au self et à ses différentes composantes selon la nomenclature de Prebble et collaborateurs (Prebble et al., 2013), dont le modèle nous a paru le plus holistique. Les auteurs décrivent le self selon un axe de subjectivité et un axe de temporalité, desquels résultent quatre composantes organisées de façon hiérarchique. Le sens subjectif de soi correspond au self subjectif dans le moment présent, et dispose d'un niveau de conscience extrêmement subtile, capable de détecter les signaux physiologiques les plus profonds, tels que les battements cardiaques ou encore d'analyser sa propre pensée grâce à ses capacités de métacognition. Il représente la composante du self la plus élémentaire, sur laquelle reposerait les trois autres composantes. Le self-conceptuel correspond au self objectif dans le moment présent et fait référence à la façon dont nous nous représentons qui nous sommes (e.g. je suis franco-suisse, neuropsychologue, sportive, brune). La continuité phénoménologique correspond au self subjectif à long terme et est associée aux aspects épisodiques de la mémoire autobiographique (e.g. je me souviens encore du jour où nous nous sommes rencontrés avec mes directeurs de thèse. J'attendais mon tour dans la salle d'attente de l'hôpital de jour gériatrique, impatiente de pouvoir leur exposer mon projet. C'était l'hiver et il faisait sombre à travers la fenêtre, mais la chaleur dans la pièce était réconfortante), par opposition à la

continuité sémantique qui correspond au self objectif à long terme et fait référence aux aspects sémantiques de la mémoire autobiographiques, dépourvus de contexte spatio-temporel précis (e.g. durant mes années de doctorat, je travaillais entre les campus de l'hôpital civil, de l'hôpital de la Robertsau et de l'hôpital de Hautepierre. Je me rendais au travail à vélo.). Si la notion de self peut paraitre vaste et insaisissable de prime abord, la contribution neuroscientifique a permis d'en faire émerger une réalité presque matérielle en y associant des substrats neuroanatomiques, bien que les réseaux cérébraux spécifiques du self conservent une certaine opacité. Alors que différentes régions cérébrales semblent héberger les traits de personnalité et les souvenirs personnels, une région spécifique pourrait sous-tendre différentes dimensions du self. En effet, l'insula qui attire la curiosité dans le monde de la recherche les dernières années, semble impliquée dans de nombreux processus, notamment sensorimoteurs, socio-émotionnels et cognitifs, permettant conjointement l'émergence de la conscience. Si son rôle central dans la conscience de soi semble évident à des niveaux élémentaires, la question n'a pas encore été approfondie à des niveaux plus élaborés. L'étude de l'insula et du Self a fait l'objet d'une revue de la littérature qui est présentée ci-dessous.

biology

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Review

Me, Myself and My Insula: An Oasis in the Forefront of Self-Consciousness

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Simple Summary: The insula, or the fifth lobe of the brain, is involved in a wide variety of functions, including processes related to the self. The self is a complex construct comprising both a subjective–objective dimension and a temporal dimension. However, because of the lack of direct investigation, it remains unclear the way the insula is involved in the different aspects of the self. This review describes the insula from both an anatomical and a functional point of view, the self through its different dimensions and the way the insula is involved in the self, relying on studies in healthy controls and in various affections. Understanding the link between the insula and the self might lead to improvement in care provision.

Abstract: The insula is a multiconnected brain region that centralizes a wide range of information, from the most internal bodily states, such as interoception, to high-order processes, such as knowledge about oneself. Therefore, the insula would be a core region involved in the self networks. Over the past decades, the question of the self has been extensively explored, highlighting differences in the descriptions of the various components but also similarities in the global structure of the self. Indeed, most of the researchers consider that the self comprises a phenomenological part and a conceptual part, in the present moment or extending over time. However, the anatomical substrates of the self, and more specifically the link between the insula and the self, remain unclear. We conducted a narrative review to better understand the relationship between the insula and the self and how anatomical and functional damages to the insular cortex can impact the self in various conditions. Our work revealed that the insula is involved in the most primitive levels of the present self and could consequently impact the self extended in time, namely autobiographical memory. Across different pathologies, we propose that insular damage could engender a global collapse of the self.

Keywords: insula; self; interoception; autobiographical memory

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1. Introduction

What makes us feel unique, living in the same body all life long, and what makes our life stories arise, is what we can call the self. The self has different dimensions, such as a physical one—the body as a whole or within its different parts—and a mental one—the first-person perspective of the self, existing and acting in the present time, and also knowledge of the self, including episodic and semantic memory knowledge. Different nomenclatures of the self exist, converging toward a hierarchical conception that ranges from the most internal bodily phenomena of awareness to very specific details of autobiographical memory. However, the anatomical substrates from which the self emerges in the brain remain unclear. A body of research suggests that a network of right frontoparietal structures is deeply involved in generating awareness, for instance, the right frontal and parietal lobes provide the ability to recognize the self-face, the self-body but also the self-voice [1,2]. These regions are therefore known to overlap with areas involved in the default-mode network,

notably cortical midline structures that show activity during tasks requiring self-referential processing [3]. Whereas numerous brain substrates support personality and memories, one specific structure might host the very primitive levels of the self, namely the insula. The insula, or the fifth lobe of the brain, is folded deep inside the frontal, temporal and parietal opercula. It is a multiconnected brain region, with multiple roles, notably, on the one hand, a sensorimotor processing posterior part integrating the primary interoceptive cortex and, on the other hand, a supporting and integrating anterior part based on viscerosensory responses, socio-emotional processing and cognitive functions that allow the emergence of awareness.

In this review, we begin by describing the insula from an anatomical and functional point of view. We then present the main different cognitive models of the self, emphasizing the aspects related to the present self and overviewing the aspects related to the self extended in time, namely autobiographical memory. Finally, we will describe how the insula is topographically involved in the present self, and how insular damage can impact the self.

2. The Insula

2.1. General Anatomy and Functions of the Insula

Although still not well understood, the insula has many peculiarities, both functional and anatomical. Whereas some studies in rodents suggest that insular cortex (IC) organization is rather multimodal and shaped by learning [4,5], others have argued for a topographical organization with a functional complexity increasing along a posterior–anterior axis [6]. The insula is involved in a wide variety of functions ranging from sensory and affective processing to high-level cognition. The current thinking postulates the existence of four functionally distinct regions. This is illustrated in Figure 1, with (1) a sensorimotor region in the mid-posterior insula; (2) a central-olfactogustatory region; (3) a socio-emotional region in the anterior-ventral insula; and (4) a cognitive anterior-dorsal region [7]. From a structural point of view, one can distinguish three different areas of the IC, with a heterogeneous cytoarchitecture that ranges from granular in the posterior portion to agranular in the anterior portion. The posterior and dorsal part of the IC, whose structure is close to the parietal and temporal opercula, is described as "hypergranular". The granularity progressively decreases from the postero-dorsal part to the antero-ventral part, toward an agranular cortex structure, with a predominant intermediate dysgranular part [8].

As reported by Craig, the posterior insular cortex (PIC) would rather be associated with sensorimotor processing, such as visceral sensations, autonomic control and interoception [9,10], whereas the anterior insular cortex (AIC) would support and integrate socio-emotional processing and cognitive functions [11–14]. A special feature of the AIC is the concentration of clusters of large pyramidal neurons: the von Economo neurons (VENs) [15], which are specific to mammals with well-developed socialization skills, such as hominoid primates, elephants, horses, pigs, cows and particularly certain cetaceans, such as the bowhead whale [16–18]. In addition to its intrinsically anatomical and functional complexity, the insula is a multiconnected brain region. Widespread connections are observed between both the right and left insula and other brain regions [19]. Regarding the frontal lobe, the insula has connections with the inferior, middle and superior gyri, the orbitofrontal cortex, the precentral gyrus, the frontal operculum and the subcallosal gyrus. Within the temporal lobe, the insula has connections with the superior temporal gyrus, including Heschl's gyrus, the planum temporale, the planum polare, the temporal fusiform gyrus and the temporal operculum. With regard to the parietal lobe, the insula has connections with the supramarginal and angular gyri, the postcentral gyrus, the precuneus and superior parietal lobule and the parietal operculum. The insula also supports connections with the occipital lobe, notably the cuneus and lingual gyri and the occipital fusiform gyrus. Finally, the insula has connections with limbic areas, such as the thalamus, the amygdala, the hippocampus and parahippocampal gyrus, including the perirhinal and entorhinal cortices, the uncus and the posterior and anterior cingulate gyri, the latter comprising VENs.

More precisely, there appear to be structural connectivity differences between the AIC and the PIC, and other brain regions. For instance, the AIC has a greater number of connections to anterior cortices (perigenual and subgenual anterior cingulate, anterior midcingulate, orbitofrontal, frontal and anterior temporal cortices), while the PIC has a greater number of connections to posterior cortices (dorsal posterior cingulate, posterior midcingulate, posterior temporal, sensorimotor, parietal and occipital cortices). However, both the anterior and the posterior part of the insula have connections with other limbic areas, such as the parahippocampal gyrus, including the entorhinal and perirhinal cortices, as well as the uncus [19–23]. Interestingly, the IC, and more precisely the AIC, is also anatomically and functionally connected to the infratentorial region of the brain, such as the brainstem, and particularly to specific nuclei: the nucleus tractus solitarii, the dorsal motor nucleus of the vagus, the parabrachial nuclei (sensory) and the periaqueductal gray (motor) [24–27]. The numerous connections found between the insula and other brain regions are consistent with the wide range of brain functions related to the insula. More broadly, insular connections with the frontal lobe have a role in language processes and in executive processes [28,29] involving an affective component, notably risk decision making [30]. Connections with auditory areas within the temporal lobe are related to the involvement of the IC in central auditory processing [31], whereas connections with parietal areas indicate a role in body scheme representations [32,33]. Insular-occipital connections, however, might be involved in emotional facial expression recognition [34]. Finally, the close relationship between the insula and the limbic system highlights the insula's involvement in emotional processes; indeed, some researchers even consider that the insula constitutes an integral part of the paralimbic or limbic system [31]. The connections to the brainstem and diencephalon involved in interoception and homeostasis will be further discussed (see Section 2.2).

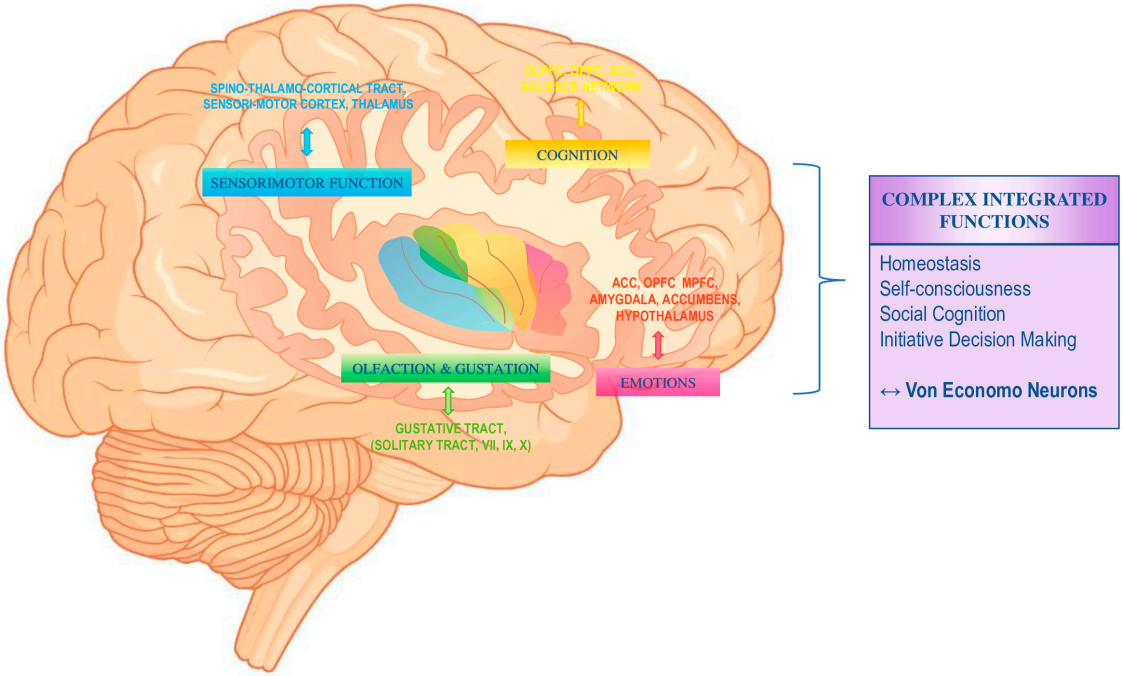

Figure 1. Functions and structural connectivity of the human insula. The blue section represents the sensorimotor function, the dark green section represents the gustatory function, the light green section represents the olfactory function, the yellow section represents the cognitive part, the red section represents the socio-emotional part and the purple section represents the complex integrated functions, stemming from the interaction of several of these functions. ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex; OPFC, orbitofrontal cortex. Adapted from "Icon Pack—Neuroscience", by BioRender.com (2020). Retrieved from https://app.biorender.com/biorender-templates, accessed on 9 April 2023.

Given such diversity, both anatomical and functional, a question arises in the context of the self: through which processes can phenomena such as the interoceptive states of the body reveal socio-emotional states and give rise to such highly elaborated functions as awareness?

2.2. From Viscera to Insular Cortex

Among the preliminary work conducted on the role of the human insula was the seminal work by Wilder Penfield, using electrocortical stimulation, in the mid-20th century [10]. Penfield notably pointed out that stimulation of the PIC elicited a variety of visceral sensory—thus prompting researchers to dub the insula the "visceral brain"—and motor responses, as well as somatic sensory responses in the face, tongue and upper/lower limbs. Interestingly, stimulation of the insula unilaterally caused a sensation on the opposite side of the body but also sometimes on both sides of the body [35,36]. The insula is considered a primarily visceral-somatic region, but beyond visceral information processing, it has been proposed that the insula plays a broader role in interoception, i.e., the sense of the physiological condition of the body [37]. The interoceptive sensations arising from the body allow for a continuous monitoring of the state of the body through mechanisms, such as heart rate, blood pressure, respiration, proprioceptive signals and visceral activity [38,39]. Among the pioneering work on the functions of the insula, Penfield and Faulk found that stimulation of the lower part of the PIC produced abdominal sensations (e.g., "gurgling", "rolling", "pain", "nausea" and "scratching") and objective evidence of intra-abdominal motor activity (e.g., "borborygmus", "belching" and "vomiting"), suggesting that the inferior PIC might monitor the sensory aspects of the stomach as well as gastric motility [35]. Nonetheless, to make the individual aware of all these sensations, the information concerning the internal state of the body is conveyed through a dedicated spinothalamocortical afferent system [40]. Interoceptive information travels within the nervous system in the form of a signal that is transmitted by several pathways and nuclei. A major component of this system consists of the Aδ and C fibers, whose role extends far beyond solely "pain and temperature" sensations. This system relates homeostatic information from all tissues of the body, innervates them and terminates monosynaptically in lamina I of the spinal and trigeminal dorsal horns. The signal therefore enters the spinal cord and trigeminal nucleus in the brainstem and conveys signals from the body structures of the head, the oral cavity, the skin of the face and scalp and the facial muscles of emotion and jaw movements to the posterior part of the ventromedial nucleus (VMpo) in the thalamus [41,42]. The VMpo anteriorly adjoins the basal ventromedial nucleus (VMb), which receives direct inputs from the nucleus of the solitary tract (NTS), within which parasympathetic afferents are carried (vagal and glossopharyngeal nerves). The VMpo and VMb then project to the PIC, progressing through the different portions of the insula. According to Craig and other researchers, Refs. [43,44], within the PIC, the interoceptive pathway produces a topographical representation of the body, from anterior to posterior aspects. The interoceptive signal is then integrated into the middle insular cortex (MIC), which has connections to the amygdala and hypothalamus, thus forming a combined representation of homeostatically salient features of the individual's internal and external environment [34]. Direct stimulation of the MIC in the inferior part might be involved in a sense of unreality [36]. The AIC is reported to be an integrative site that represents "a common neural substrate for embodied and experiential processes" [45]. More specifically, the right AIC has been explicitly implicated in the mapping of the interoceptive state and response to heartbeat detection tasks, which are relevant tasks to assess visceral sensitivity [46]. The AIC constitutes a coordination site for "high-level homeostatic information, perhaps on the general state of the body, which is an important component of emotional experience and a sense of well-being" [47]. Picard et al. showed that electrical stimulation within the anterior-dorsal insula induces an intense feeling of bliss, involving both emotional and interoceptive components [13]. Thus, the AIC is involved in the representation of "cognitive feelings" which arises from the moment-to-moment integration of homeostatic information emanating from the body [40].

It has been further proposed that the AIC "instantiates all subjective feelings from the body and feelings of emotion" [6]. By generating an analogous "re-representation", the AIC provides a basis for the subjective evaluation of the interoceptive state, which is therefore routed to the orbitofrontal cortex, a center of hedonism assessment. Finally, emotional experience and awareness occur as an emergent process across systems.

2.3. From Interoception to Awareness

Interoception is an active process that forwards neural information from the body to the brain and regulates vital processes at the most elementary level, while also modulating emotional experience. Bodily feelings are reported to be at the core of bodily awareness and even of the self [43,48,49]. Bodily awareness refers to the conscious perception of somatic and internal sensations and to awareness that these experiences are bound to the self [50–54]. It is a multidimensional construct that involves the feeling of owning a body and being the agent over one's own actions [50–52].

As theorized by Craig [6,39], the sense of self results from a "cortical (that is, mental) integration of salience across all conditions", at any moment in time, which constitutes homeostatic processes that determine what is salient to the individual. The foundation of Craig's model is the perception of interoceptive neuronal signals as sensations, or "cognitive feelings" [39], through the creation of re-representations. Such signals generate pain, temperature, thirst, hunger, itch, muscle burn or ache, sensual touch, visceral urgency, flush and nausea, among other sensations [38]. Numerous studies have reported that the concept of the re-representation of the interoceptive condition of the body serves as a limbic sensory substrate for subjective feelings. Such studies show that activation in the right AIC and orbitofrontal cortices are associated with subjective emotion (e.g., recall-generated sadness, anger, anticipatory anxiety and pain, panic, disgust, sexual arousal, orgasm, trustworthiness and responses to music [55–61]) and that the right AIC is thus a fundamental structure for the generation of the mental image of one's physical emotional state. The posterior-to-anterior anatomical model of integration from the primary interoceptive representations to the absolute representation of one's feelings strongly suggests that awareness relies on homeostasis [40,62–64]. These data are consistent with Antonio Damasio's hypothesis of the "somatic marker" which suggests that the subjective process of feeling emotions recruits brain regions that are involved in homeostasis. These feelings we perceive are the basis of our perceptions of ourselves, distinguishing between what belongs to the internal world and what belongs to the external world, and thus provide a neural basis to distinguish the self from the non-self. By integrating the interoceptive representation into a re-representation, the right AIC has the capacity to perceive the self as a physical and separate entity, in other words, subjective awareness. Thus, when first describing the intracerebral stimulation of the right insula, a patient might say, "I feel myself going" [35].

In the next section, we will focus on the different models of the self, before describing more precisely how the insula is involved in the different aspects of the self.

3. The Self

"I think, therefore I am". Sense of self is an essentially human characteristic that provides one with the feelings of singularity, coherence, individuality and unity [65]. It is the mental process that unifies disparate experiences, levels of awareness, behaviors, cognitions and mental representations into a coherent, unified whole [66,67]. In common discourse, the term "self" refers to a feeling that something is "about me". Reflecting on oneself requires that there is an "I" that can consider an object that is "me". The question of the self has been widely explored by philosophers and psychologists. At the end of the 19th century, William James made an inventory of the physical self, mental self, spiritual self and the ego [62]. He distinguished the psychological process that is the subject of knowing and experiencing (the I-self) and the object of this awareness (the Me-self). His theory, heuristically of tremendous value, has dominated discussion around the sense of self and has been variously supplemented. For instance, Neisser suggested important distinctions

between ecological, interpersonal, extended, private and conceptual aspects of the self [68]. These distinctions—or equivalents—reappear in more recent theories of the self as discussed in the neuroscience and neuropsychology fields, notably by researchers such as Antonio Damasio, Shaun Gallagher and Sally Prebble [48,65,69,70]. Different models emerged from their theories and hypotheses, but these present nuances rather than major differences (see Figure 2). As proposed by James in his pioneering work [62], more recent models support the idea that there is a phenomenological self (i.e., the I-self) and a conceptual self (i.e., the Me-self). The I-self refers to the subjective living experience that contributes to the construction of a mental representation of the self [71–74], whereas the Me-self supports the object of this representation, including knowledge about ourselves [74,75]. To complete William James' work, most researchers have added a temporal dimension to their conception of the self that distinguishes the present self and the temporally extended self. The present self refers to the aspects of the sense of self that are related to and accessible in the present moment. As mentioned above, the temporally extended self refers to autobiographical memory and brings out the feeling of being the same person over time despite changes. In this review, we briefly overview the temporally extended self—or autobiographical memory—and we mainly focus on the present self, numerous aspects of which seem to be supported by the insula (see Section 3. Insula and the present self). The main theses are presented and discussed below. We focus particularly on Prebble's model, which seems to be the most exhaustive, and we use its nomenclature to refer to the different components of the self. The authors approach the self along a subjectivity axis and a temporality axis, which give rise to four distinct components with different levels of awareness: the subjective sense of self (SSS), the self-concept (SC), the phenomenological continuity and the semantic continuity.

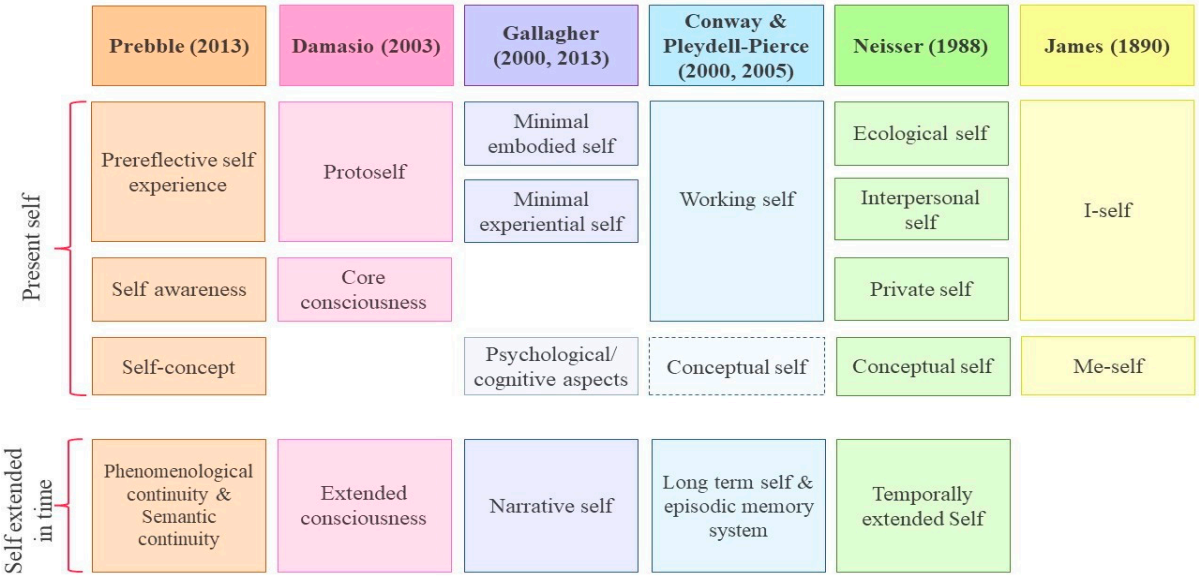

Figure 2. Synthesis of the main models of the self and autobiographical memory, with correspondences between the principal components. The orange frames depict Prebble's model (2013), the pink frames depict Damasio's model (2003), the purple frames depict Gallagher's models (2000; 2013), the blue frames depict Conway and Pleydell-Pierce's models (2000, 2005), the green frames depict Neisser's model (1988) and the yellow frames depict James's model (1890).

3.1. The Present Self

On the one hand, the present self supports the SSS, which is the phenomenological part involving multiple levels of awareness. On the other hand, the present self supports the SC, which is the semantic part and involves the collection of knowledge about oneself [65].

3.1.1. The Subjective Sense of Self

Prebble and collaborators also refer to the SSS as "the I-self", as initially proposed by James [62]. The SSS constitutes the most elementary aspect of the sense of self. Humans would appear to share this component with most animals endowed with complex brains and sensory organs [6]. It is the component that confers the feeling of living in the present moment as a sentient being and is the cornerstone of the sense of self that allows the other components to exist and thereby makes possible the existence of autobiographical memory in humans.

In Prebble and collaborators' model, the SSS is made up of two hierarchically related forms of present-moment conscious self-experience: prereflective self-experience and self-awareness [65]. Prereflective experience refers to what some philosophers call "Qualia" and is related to an immediate and ongoing sensory or perceptual stream of experiences [69,76,77]. It can be understood as an integral feature of our conscious experience of the world [78,79]. In Neisser's theory, the prereflective self-experience corresponds to the "ecological self" and the "interpersonal self". The ecological self refers to self-body awareness and recognition, while the interpersonal self implies the feeling of agency. Damasio's equivalent is the "protoself"—a pre-conscious state representing the first stage of the hierarchical process of awareness generation. The protoself refers to a collection of neural patterns that are representative of the body's internal states. This aspect of the self constantly detects and records the internal physical changes that affect the homeostasis of the organism [80]. For Gallagher, the SSS corresponds to both a "minimal embodied self" and a "minimal experiential self". The first one includes core biological and ecological aspects, which allow the system to distinguish between the self and the non-self. The second one contributes to an embodied sense of ownership (i.e., confers the feeling that I am the one undergoing the experience) and a sense of agency (i.e., confers the feeling that I am the one who is initiating or causing an action) [70]. Regarding the second component of the SSS in Prebble's model, self-awareness reflects the ability to introspect about one's mental states, behavior and experiences [81–83]. It represents a higher and reflective level of awareness that implies two important features. First, awareness is supposed to be directed inwardly, as opposed to toward the external environment [72,74,75,84–86]. Second, it is a reflective and meta-conscious experience that involves a capacity to observe, reflect, evaluate and focus attention on one's subjective experience [72,74,75,82,87,88]. The equivalent is referred to as the "private self" in Neisser's model and is based on awareness that the conscious experiences are exclusively our own. Damasio uses the expression "core consciousness" to refer to when the perception of the external world becomes conscious. He describes it as an emergent process that occurs when an organism becomes consciously aware of feelings associated with changes in internal bodily states [48]. Gallagher does not discuss this level of consciousness in his models. In the self-memory system (SMS) of Conway and Pleydell-Pierce, the authors consider the present self as a one and only component they call the "working self", which is a sort of dynamic cognitive structure that acts as a central control process and modulates access to another component which is the long-term self.

The SSS, and especially the prereflective experience, is particularly difficult to evaluate. One way to measure it consists of assessing interoception, and some studies (see, infra, Sections 4.1.1 and 4.1.2) have shown that it would be mainly based on the insula and on medial subcortical structures, such as the hypothalamus, which controls the general homeostasis of the organism, and the brain stem, whose nuclei map body signals [66]. Concerning self-awareness, a large range of neural regions are reported to be involved, including the following: cortical midline structures, such as the cingulate, medial prefrontal and parietal cortices; lateral cortical regions, such as the insula, the lateral prefrontal and parietal cortices and the temporal poles; and subcortical regions, notably the hypothalamus, the brainstem, the colliculi and the periaqueductal gray [89].

The SSS is a reflective process that is assumed to involve the construction of mental models of the self: the objective Me-self or SC.

3.1.2. The Self-Concept

The SC is made up of autobiographical knowledge and refers to the way we internally represent who we are, determining what sort of person we are. According to Prebble's model, the SC relies on all the attributes, traits, beliefs, values, social status, roles and physical characteristics we attribute to ourselves (e.g., I am a neuropsychologist, my hair is brown, I am French) but also contains self-esteem, self-image, goals, behavioral scripts and schemas and information about one's material possessions and social relationships [62,65,68,90]. For most cognitive scientists, the SC is part of the present self but is highly dependent on autobiographical memory, which contributes to both the formation and maintenance of our knowledge about who we are [91–97]. In his 2013 model, Gallagher evokes some "psychological/cognitive aspects" of the self, which he describes as ranging "from explicit self-consciousness to conceptual understanding of self as self, to personality traits of which one may not be self-conscious at all", but he also proposes to include the ability to represent oneself as oneself, while supporting the idea that psychological continuity and memory are important for personal identity [70]. Damasio's theory does not isolate an SC component per se. In his view, there is an autobiographical self that emerges in extended consciousness, which he depicts as "a relatively stable collection of the unique facts that characterize a person" [98]. Conway, on the other hand, considers that the SC exists independently of specific, temporally defined incidents. However, in his model, he opted to integrate the SC in the long-term self because abstracted knowledge structures have to be connected to autobiographical knowledge and the episodic memory system to activate specific instances that exemplify, contextualize and ground their underlying themes or concepts [90]. He also postulated that memories from adolescence and early adulthood, known as the "reminiscence bump", have significant influence in supporting self-knowledge, notably because during this time a greater number of memories that are relevant to identity formation are encoded and remain highly accessible for later retrieval [99–101]. However, there is no evidence that memories are essential to the formation of conceptual self-knowledge, and other perspectives suggest that our conceptual self-knowledge may be "computed" at any given moment with relevant behavioral exemplars from autobiographical memory (e.g., remembering having long conversations makes me think I am talkative). Another possibility is that conceptual self-knowledge is independent of autobiographical event memories [94,95,102], which means that there would be no need to reference past events stored in autobiographical memory to access an abstracted mental representation of ourselves (e.g., I am talkative). This view is further supported by neuropsychological case studies showing that individuals with severe episodic memory impairments still retain accurate knowledge about their personality traits [103–107]. Certainly, one of the most famous cases is that of patient KC, who suffered severe retrograde and anterograde episodic memory loss following a motorcycle accident and, despite undergoing dramatic personality changes and having no memory for any events from his past, could reliably report his post-accident personality [107]. However, the hypothesis that conceptual self-knowledge and autobiographical event memories are independent is only relevant to a very specific form of conceptual self-knowledge: personality traits. Further studies, which examined other varieties of self-knowledge, such as social roles, physical attributes, values and preferences, suggested that episodic memory might play a role in maintaining these aspects of the conceptual self [92,108]. Concordant with the case of patient KC, these studies show that neither the formation nor the maintenance of abstract trait self-knowledge, such as personality traits, relies on episodic memory. First, having accurate knowledge of one's personality traits does not depend on the ability to retrieve episodic memories of the events that led to the creation of self-belief. Second, it is possible to form new beliefs about one's personality traits without the ability to encode new episodic memories [104].

As suggested by Conway's theory and supported in Prebble's model, semanticized autobiographical memory might play an important role in forming and maintaining the conceptual self, including knowledge at the level of life story, life chapters and general events [65,90,91]. Conceptual self-knowledge is therefore likely to be stored as part of the

semantic memory system [94,102,109,110] but appears to recruit distinct neural regions from episodic and semantic autobiographical memory [110]. Faculties such as personality traits, skills and physical characteristics are reported to rely on medial cortical structures, such as the dorsomedial and ventromedial prefrontal cortices, anterior and posterior cingulate cortices, median parietal cortices, temporal poles and insulae [111–122]. In addition, studies on SC have shown that some subcortical regions are also involved, such as the brain stem, colliculi, periaqueductal gray, hypothalamus and hypophysis [89,123,124].

3.2. The Self Extended in Time, or Autobiographical Memories

The idea of the self extended in time pertains to autobiographical memory, which progressively develops over time. Prebble et al. support that the self extended in time is the continuity of the self across time, meaning that, despite change, one continues to be the same person now as in the past, and will continue to be the same person in the future [65]. They suggest the existence of two kinds of self extended in time: autobiographical episodic memory and autobiographical semantic memory. The episodic version of autobiographical memory is based on Tulving and colleagues' princeps work on autonoetic consciousness [125–127]. Autonoetic consciousness refers to the capacity to mentally travel through time, relive past experiences in an extremely vivid way and project oneself and one's forward behaviors into the imagined future, based on past experiences. For instance, "I remember that evening in December when I had dinner in the tallest building in Montreal with a panoramic view; I was sitting near the window at the back, in the right-hand corner of the restaurant, and it was freezing". Tulving uses the term "remembering" to refer to autonoetic consciousness, which also encompasses the ability to project oneself into the future, based on one's previous experience. "On my next trip, I would like to go back there, but this time I would rather sit in the middle of the restaurant, close to the fireplace". Autonoetic consciousness is a defining property of episodic memory and a fundamental ability in the formation of our self-identity, which confers the feeling of being the same subject reliving a memory as the one who lived the event. Researchers suggest that autonoetic consciousness provides subjective experience phenomenological continuity which reminds us of the perceptions, thoughts and emotions that accompanied the original experience [65,77,126–129]. Therefore, episodic autobiographical memory allows one to build oneself as a constant evolving individual and plays a key role in the maintenance and the continuity of self. Nonetheless, the relationship between the present self and its extended-in-time equivalent is bilateral, as the "online" self makes autobiographical memory emerge. This might explain why we have no—or only very approximate—memories of early childhood: we would be able to encode knowledge that can then form autobiographical memories at about 24 months, when developing our "cognitive self" (i.e., SSS) as indexed by visual self-recognition [130,131].

The semantic version of autobiographical memory is supported by three different forms of semantic continuity [65]. The "semantic temporal chronology" would support a conceptual understanding of oneself as a temporally extended being and requires a preserved semanticized autobiographical memory. Semanticized autobiographical memory refers to memories initially strictly episodic or "specific" that have lost their contextual details and become "semanticized"; these are, for instance, summaries of repeated or extended events over time (e.g., "for the past decade, my friends and I have been getting together every year to go to the music festival 'les Eurockéennes'. Each time, we camp at a different friend's place and have barbecues that go on forever during the day, and then we go to the festival to listen to the concerts in the evening"). It may also play a vital role in facilitating a personalized chronology, including allowing one to imagine a personalized future, by providing the frame that allows episodic memory details to be recombined into novel future scenarios [132] (e.g., "This summer, the festival has been canceled because of the COVID-19 epidemic, but we are still able to get together for the weekend at a friend's place, to camp and have barbecues, which, this time, will last all day and all night in a festive and authentic way, all with a musical backdrop"). The second form of semantic

continuity is a "temporally extended SC". The richness and sophistication of the SC make it resistant to change; thus, self-knowledge may provide a persistent model of self that would raise a sense of continuity, through the construction of a temporal chronology of our conceptual knowledge (e.g., "since I was a child, I've always loved music") [71,91,109]. The conjunction of semantic temporal chronology and temporally extended self-knowledge leads to the third form of semantic continuity, namely the "narrative continuity" which is related to our life stories. The life story refers to the way we thematically and temporally organize information about our lives [133]. It is a narrow selection of autobiographical memories that collectively explain "how I came to be who I am" (e.g., when I was at University, I always got around by bike, and I realized it was a fast and ecological way to travel. Today, I only use my bike to go to work) [65,134]. Prebble's vision of the self extended in time is highly elaborated, postulating several parallel mechanisms that allow episodic and semantic autobiographical memory to exist. Another exhaustive vision of autobiographical memory is Conway's, which suggests that autobiographical memory arises from a combination of the episodic memory system and the long-term self [90]. Indeed, in the modified version of the SMS, the author proposes to integrate the long-term self, which implies the conceptual self that we cited above assimilated to the SC as it is classically depicted, and the autobiographical knowledge base. The autobiographical knowledge base itself consists of three broad areas: "lifetime periods", which reflect overarching goals and activities (e.g., when I was at University, when I lived in Montreal); "general events", which are categories of events linked across brief time periods (i.e., a week, a day, a few hours) or organized by a shared theme (first-time experiences, academic meetings); and "life-story schema", which consists of an individual's understanding of how the normative life story is constructed within our culture (e.g., my life as a woman in the 21st century, or my career as a hospital neuropsychologist).

Some other researchers have a more general conception of the self extended in time. Neisser describes it as "the self as it was in the past and as we expect to be in the future, known primarily on the basis of memory" [68]. Gallagher shares such a vision; in his view, the narrative self is extended in time to include memories of the past and intentions toward the future [69]. In the case of Damasio, the "extended consciousness" is the third and final layer of his model. He describes it as "a relatively stable collection of the unique facts that characterize a person, the 'autobiographical self'" that depends on memories of past situations.

The anatomical substrates of both episodic and semantic autobiographical memory have been extensively explored in neuroimaging studies. The episodic form mainly relies on the brain networks that allow mental travel across time to retrieve memories, namely the hippocampus, which mediates recollection, and the posterior medial cortices, which support the visuospatial context processing of events, notably the temporo-parietal junction, the posterior cingulum, the precuneus and the retrosplenial cortex [92,135–139]. The semantic component of autobiographical memory notably involves the lateral temporal structures, and in particular the middle temporal gyrus, which is associated with general autobiographical knowledge related to personal events [140–145]. Finally, the insula would play a role in the foundation and primitive aspects of the self rather than in its extended conception. Based on this hypothesis, we suppose that damage to the insulae, and, consequently, eventual impairments of the most elementary components of the self, might therefore impact both episodic and semantic autobiographical memories.

4. Insula and the Self

The previous two sections reviewed the anatomical and functional aspects of the insula and depicted the self according to its main characteristics and through the eyes of different scientists. Here, we will mainly focus on the relationship between the insula and the present self. Indeed, only a few studies have been conducted so far on the self extended in time, i.e., autobiographical memory, in patients with insular damage, leaving only hypotheses regarding the relationship between the insula and the self extended in time.

4.1. Insula and the Subjective Sense of Self

As stated above, the IC is reported to be involved in processing a variety of bodily sensations, notably those related to interoception [40], leading to the assumption that the insula plays a role in generating core self-states. How is the insula involved in the SSS? Additionally, in what way does its impairment lead to an alteration in the SSS?

4.1.1. Subjective Sense of Self in Healthy Insula

Very little work has focused on the link between the subjective experience and the insula. This is partly because of the difficulty in assessing the subjective experience. However, there is some evidence to suggest that the insular cortices are particularly involved in the SSS, from the deepest internal states of the body that we can perceive via interoception to metacognition capacities [1,49].

The assessment of interoceptive accuracy is performed by tasks assessing the individuals' precision in monitoring their body activity, such as the heartbeat detection or heartbeat counting task [146,147]. For instance, a study conducted by Critchley demonstrated that the performance on interoceptive accuracy tasks was significantly and positively correlated with functional activation within the right IC and operculum, and that both the performance on the heartbeat detection task and the score on the subtest of the body perception questionnaire assessing awareness of bodily processes correlated with gray matter volume within the same regions [46]. Accordingly, a meta-analysis of neuroimaging studies found that interoceptive accuracy was associated with an increased activation of the IC, the somatosensory cortex, the precentral gyrus and the inferior frontal gyrus [148]. Moreover, a research team focused on non-painful gastric distention and showed that a subjective sense of fullness was associated with activation peaks in the bilateral dorsal PIC, the left MIC, the left AIC and the anterior cingulate cortex (ACC) [149]; such results therefore support the posterior to mid-anterior pattern of integration, from unconscious internal bodily states (i.e., stomach distention) to the interpretation of interoceptive sensations (i.e., satiety sensation). Another study revealed the involvement of the bilateral PIC and middle insulae when participants were aware of their own heartbeats, with right hemispheric dominance [148]. Beyond interoceptive accuracy, Critchley's study found a strong relationship between negative affect and the blood-oxygen-level-dependent response in the right insula [46], thus supporting the proposal that the insula mediates interoceptive awareness and contains representation of bodily reactions in response to affective feeling states, in other words, somatic markers [48]. The higher-order somatosensory function, such as a subjective sense of body ownership, seems to be associated with the right IC. In an experiment using the rubber-hand illusion paradigm, Tsakiris and collaborators reported a positive correlation between activity in the right PIC and the sense of body ownership during the rubber-hand illusion, in which the subject was not actually moving but felt that the moving hand was their own [150]. However, Farrer and collaborators investigated the neural signatures of the sense of agency, using similar methods, such as the systematic manipulation of visual feedback to alter the experience of one's body in action. They demonstrated that activity in the right PIC was correlated with the degree of matching between the performed and the viewed movement, and thus with self-attribution [151]. Beyond its involvement in the most primitive aspects of the SSS, the right insula seems to be implicated in more highly elaborated levels of awareness, such as visual self-recognition in comparison with the processing of another, highly familiar person's face [152,153]. Moreover, in an experiment where subjects had to pass judgment between a self-referential condition versus a control condition in response to affectively normed pictures, the activation in medial areas, notably the bilateral insulae, was found in the condition requiring reflection on one's emotional state, thus supporting a role in emotional awareness [154]; the authors even emphasized the role of medial areas in the integration of visceromotor aspects of emotional processing, with information gathered from the internal and external environments. Another study illustrating the relationship between interoceptive experience and emotional context highlighted correlations between activation, predominantly within the left dorsal ACC and

bilateral AIC, and the intensity of negative context [155]. This implies that emotional states are integrated with interoceptive states in the representation of the subjective feeling of the moment.

4.1.2. Subjective Sense of Self in Damaged Insula

As previously described, the insula receives data from all sensory modalities and has strong connections with both the limbic and autonomic systems, allowing one to create an awareness of one's physical self now and across time. In other words, the insula by itself has a role in interoceptive awareness, namely what allows us to feel, understand and construe what is happening deep inside our bodies. Consequently, dysfunction of the insula is likely to lead to abnormal subjective feeling states and disrupt the SSS.

Meta-analyses of functional and structural studies are converging on a "common core" of areas that are affected across several psychiatric conditions [156,157]. Numerous studies reported significant gray matter decreases in the dorsal ACC and bilateral AIC in individuals with psychotic (i.e., schizophrenia) and nonpsychotic conditions (i.e., major depressive disorder, bipolar disorders, obsessive-compulsive disorder, substance use disorder and several anxiety disorders) [157]. For instance, a study found that patients remitted from anorexia nervosa showed reduced activation when hungry in the AIC and reduced functional connectivity between the right AIC and mid-dorsal insula and ventral caudal putamen, compared to healthy controls [158]. Such a disconnection could lead to failure in integrating taste information with homeostatic but also motivational drives. Interestingly, Naqvi et al. showed that insular damages diminished addictive behaviors, suggesting that it might be the result of a reduced ability to detect interoceptive states related to craving or a reduction in the hedonic feeling induced by the substances [159,160]. Concerning the involvement of the IC in psychotic conditions, it has been demonstrated that among populations at high risk for developing schizophrenia, subjects who go on to develop psychosis have decreased insular gray matter initially, compared to those who do not become psychotic [161,162]. Likewise, bilateral decreases in insular gray matter volumes are associated with schizophrenia with both positive and negative symptoms, possibly due to the misperception of the self as a distinct entity from the external world [163–166]. Furthermore, it has been demonstrated that lesions of the right PIC disturb the sense of limb ownership, leading to the sensation that a contralesional limb does not belong to one's own body or even belongs to another person [167]. In addition to structural anomalies, the insula response during the processing of emotional facial expressions is abnormal in schizophrenia, and this process appears to involve functions subserved by the AIC, such as evaluating emotions, empathy and the theory of mind [168–170]. Thus, there seems to be a strong relationship between insular damage and mechanisms allowing one to distinguish what belongs to the self and what belongs to the non-self. These difficulties could reveal impairments at the level of the SSS. Neuropsychiatric symptoms reflecting perception deficits such as hallucinations and delusions have also been highlighted in patients with Alzheimer disease (AD), Parkinson's disease (PD) and dementia with Lewy bodies (DLB), correlating with atrophy in the right PIC and, to a lesser extent, in the left AIC [171]. Moreover, interoceptive disorders have been demonstrated in neurological and developmental disorders. For instance, in patients with autism spectrum disorders (ASD), self-reported poor awareness of one's own and others' feelings were associated with a reduced response in the interoceptive IC [43,46]. In another study, Gracia-Cordero et al. investigated interoceptive awareness neural correlates within a cohort of patients with behavioral variant frontotemporal dementia (FTD), AD and frontal strokes, and control subjects. Participants were asked to tap a keyboard in time with their own heartbeat and then to estimate their confidence level at performing the task. Patients with AD and FTD showed a significant deficit in their confidence in reporting biological changes, which was related to atrophy across a broad frontotemporal, parietal and limbic-insular network [172]. PD is also known to be associated with reduced interoceptive accuracy and sensibility, which might even be taken as a proxy of insular degeneration in the disease, according to

some researchers [1,173]. Another mechanism that may reveal impairments of the SSS is anosognosia. Philippi and collaborators published a case report about Henry, a patient with mild cognitive impairment due to AD who had disproportionate atrophy within the medial prefrontal cortex (MPFC) and the IC and presented unusual anosognosia [174]. In a study about memory awareness—a metacognitive function matching the self-awareness level in Pebble's model—in AD, Cosentino and collaborators demonstrated a specific role for the right insula in supporting metamemory, with gray matter volume positively correlated with metamemory accuracy [175]. In line with this, a study in stroke patients revealed that the right IC was commonly damaged in patients with anosognosia for hemiplegia/hemiparesis but significantly less involved in the same population without anosognosia [32]. Other high-order awareness processing, such as the loss of subjective emotional awareness, or alexithymia, has been related to the degeneration of VENs in the AIC in FTD patients [176]. In the same line, a study found that high-functioning people with ASD displayed increased alexithymia which was correlated with reduced activation in the AIC [177], as well as brain-injured patients with pronounced AIC lesions being likely to acquire alexithymia [178]. Moreover, finally, in a cohort of patients with various neurodegenerative conditions (i.e., behavioral variant FTD, semantic dementia, progressive aphasia, progressive non-fluent aphasia and AD), bilateral insula integrity was found to be associated with social interaction insight [179].

In agreement with Craig's work and pioneering experiments [6,35], numerous functional and structural neuroimaging studies have reported that the insula, and notably the right insula, seems to play a key role within several layers of the SSS, in both healthy and pathological subjects.

4.2. Insula and the Self-Concept

Self-related processing is known to engage several cortical regions, particularly along the midline, including the prefrontal cortex, posterior cingulate cortex and parietal regions [89]. Moreover, some neuroimaging studies have already reported insular activity, thus implying a potential link with the re-representations created by the anterior part of the insula, after analysis and interpretation of the internal bodily states that have been forwarded to its posterior part [111,180–182].

4.2.1. Self-Concept in Healthy Insula

As mentioned earlier, the SC encompasses the body of autobiographical knowledge, self-esteem and self-image and refers to the prototype we have of ourselves. Therefore, it makes sense to consider that the insular region is involved in such processes, given the nature of its multiple connections with numerous brain regions, especially the ones associated with the limbic system, which is involved in the formation of memory and, consequently, of personal identity. Northoff et al. reviewed functional imaging studies of self-related tasks, namely tasks involving the judgment of personality traits, goals, abilities and physical appearance, which pertain to the SC. The authors emphasized the implication of the cortical midline structures, including the MPFC, the temporal poles and the IC [89]. In another study, Modinos and colleagues highlighted a major involvement of the left AIC, among other regions, and notably those associated with the limbic system, such as the MPFC and the anterior cingulate cortex, when subjects were engaged in self-reflection rather than when they reflected upon an acquaintance or general knowledge [111]. Interestingly, Kircher and collaborators found that the left side of the insula is involved in the content of self, such as self-knowledge of personality traits [153]. Another study about self-referential and social processing found a positive correlation between the degree of self-relatedness and activation in the left AIC—among other "core self" regions, such as the MPFC and the posterior cingulate cortex [183]. Interestingly, Perini and collaborators' work about social salience of the self in adolescents found activations in the right AIC and dorsal ACC, when the evaluations were directed toward the self rather than others [184].

Thus, it is well-established that the AIC is a main actor in the representation of personality traits. Moreover, different patterns of activation in the insula would appear to be associated with different personality types, such as the novelty-seeking trait, which is correlated with a higher dopamine concentration in the right IC [185]. Furthermore, Johnson et al. found that an introvert personality was correlated with increased blood flow in the AIC, whereas an extravert personality was correlated with increased blood flow in the PIC [186].

4.2.2. Self-Concept in Damaged Insula

Different affections such as psychiatric and neurologic disorders or acquired brain injury can affect the IC or interconnected structures, and therefore the SC.

A study conducted by Cicero et al. explored SC consistency, stability and clarity in patients with schizophrenia, a condition in which insular dysfunction is known to exist [156,157]. For this purpose, they used the Self-Concept Clarity Scale [187] and the Me-Not-Me Decision Task [188]. In the first task, participants had to rate statements (e.g., "My beliefs about myself often conflict with one another") on a scale from "Strongly Agree" to "Strongly Disagree"; in the second task, participants had to decide whether or not 60 adjectives described themselves. Compared to healthy controls, the researchers observed that patients with schizophrenia, and notably patients with positive symptoms, had lower scores on the Self-Concept Clarity Scale. Moreover, they found more inconsistent responses to the Me-Not-Me Decision Task (e.g., responding "me" to both "shy" and "outgoing") in participants with schizophrenia associated with negative symptoms [189].

A few studies have examined self-perception in other conditions associated with insular dysfunction, such as ASD [103,190]. In early research, Capps and collaborators explored SC in children with ASD versus typically developing children. They found lower global self-esteem and social competences in the ASD group compared to the typically developing children [191]. Another study on SC in adolescents with ASD showed that they perceive themselves to be less competent in a variety of domains, including social, athletic and peer likability domains, compared to typically developing adolescents [192].

Other interesting models to study the SC are neurodegenerative diseases. Indeed, AD is typically characterized by personality changes, and group studies have already emphasized a deterioration of conceptual self-knowledge, which is frequently reported by patients' relatives [92,193]. In Henry's case report, Philippi et al. reported that, in addition to the SSS disorders, the patient was unable to describe his SC, nor could he recall semantic autobiographical information, despite preserved general cognitive abilities [174]. Likewise, DLB patients also present difficulties in describing their SC [194]. In another study, researchers focused on the involvement of the IC in SC, and in particular its influence on personal tastes, in patients with early-stage DLB. They found that patients presented significant changes in tastes, in both food and non-food domains, compared to matched healthy control subjects. Moreover, these changes were negatively correlated to the bilateral IC volume [195]. Similar changes have already been observed secondary to isolated right insular infarct: patients presented changes in food and clothing tastes, among other behavioral (e.g., vegetative and sensory disorders) and cognitive symptoms (e.g., social, emotional and intuitive dysfunctions) [196].

Finally, there does not seem to be a consensus about the role of the different parts of the IC in the SC, although several studies have suggested a major involvement of the left insula when it comes to thinking of information about oneself [111,153,183].

4.3. Insula and the Self Extended in Time

Previous research has shown the insula to be a core region of the present-self networks. However, little is known about its contribution in autobiographical memory processing. The insula appears only as a secondary region of autobiographical memory in a healthy population [197]. However, autobiographical memory is impaired in psychiatric conditions and neurodevelopmental disorders associated with insular dysfunction, such as schizophre-

nia and ASD [198,199]. To our knowledge, there are no studies directly exploring the link between the insula and autobiographical memory. In line with Prebble's model, and as supported by the case report of Henry who presented a severely impaired autobiographical memory, disproportionately for a prodromal stage of AD, we suggest that the dysfunction of autobiographical memory would be linked to a global collapse of the self, notably involving insular damage, through a breakdown in awareness, which has been proposed as a prerequisite for all other components of the self [65,174]. Given that the SSS and the SC are considered crucial for the formation, consolidation and maintenance of episodic and semantic autobiographical memory [65,68,98,125,131], we believe that impairments of the present self might lead, due to a cascade effect, to an alteration in the more highly elaborated components of the self, such as autobiographical memory. Future studies will need to explore the link between the components of the self extended in time and the insula. We suggest that DLB would constitute an interesting model to further support our hypothesis that insular damage engenders a global collapse of the self, with consequences for life memories. Indeed, we previously demonstrated that insular atrophy occurs bilaterally as early as the prodromal stage of DLB [200,201]. Moreover, we found that these early damages were also accompanied by a reduction in white matter volume in the brainstem [200], which is involved in the SSS [66]. Thus, we consider it likely that DLB patients would present a global impairment of the self, first related to the deterioration of the SSS.

5. Conclusions

This review has focused on the insula and its broad range of functions, the self through its different components and the relationship between the insula and the self. We have presented findings that indicate that the insula is involved in a wide variety of functions, ranging from sensory and affective processing to high-level cognition, such as processes constituting the self. Finally, scientists agree that the self exists in the present moment but also entails an extended-in-time version that refers to autobiographical memory. Moreover, they all agree on the existence of both a self as a subject and a self as an object. The link between the present self, notably as a subject, and the insula has been widely explored and is now well established. Our review found results supporting Craig's hypothesis of a posterior-to-anterior insular axis of complexity [40]. Indeed, some studies support the notion that elementary aspects of the SSS, as assessed by interoception, body ownership or sense of agency, are sustained by the PIC [148–151,167], while more highly elaborated levels of the SSS, such as metacognitive abilities and emotional awareness, are sustained by the AIC [154,155,176]. Furthermore, as proposed by Craig's work and pioneering experiments, the SSS seems to be specifically sustained by the right insula, thus suggesting that some aspects of the self could be lateralized [6,32,35,46,150–153,167,175]. Conversely, the involvement of the left insula is often reported in the literature when subjects are thinking of personal information about themselves [111,153,183], whereas the specific roles of the AIC and the PIC in the SC remain unclear. Finally, we are of the view that the insula's contribution to autobiographical memory could be secondary to its strong involvement in the present self. We propose to conduct a holistic exploration of the different components of the self, from visceral brain to life memories. The most elementary aspects of the SSS could be studied by means of tasks assessing interoceptive awareness, such as the heartbeat detection task, and for the SSS processes of higher order, by means of questionnaires assessing anosognosia. The SC could be explored via questionnaires based on self-knowledge, evaluating the idea we have of who we are. Finally, autobiographical memory could be measured through the recollection of episodic and semantic memories. Scientifically, studying the self in DLB which is characterized by early insular atrophy would enable us to characterize the anatomic substrates and the relationships between the distinct components of the self. Clinically, such an exploration would provide a better understanding of the personality changes observed in the disease, with potential benefits for both the patients and their relatives. Finally, identifying the self-impairments within this population

might lead to the development of self-focused cognitive remediation. Indeed, therapeutic research in neurodegenerative disease has not yet been successful for curative treatments. Thus, patients can mainly benefit from pharmacological treatments focusing on symptom alleviation. Hence, every way to improve cognition and quality of life for patients and their relatives must be considered, particularly non-pharmacological treatments. Therapies such as mindfulness-based cognitive therapy might help to improve elementary aspects of the self such as the SSS and consequently act upon higher-order self-components, such as autobiographical memory. Furthermore, recent studies in rodents demonstrated how the IC is plastic [202–206], thus opening new perspectives of treatments, such as repetitive transcranial magnetic stimulation, that our team is currently experimenting in DLB to explore the insula's different roles (STIMLEWY study). By identifying self-impairments and their anatomical substrates in DLB, we could use the same methods to improve self-awareness, and also more broadly global cognition, sensory abilities and even emotional states.

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CONCLUSION PARTIE 2 : À travers cette revue de la littérature, nous avons montré que le rôle de l'insula balaye une grande variété de fonctions impliquées dans le self, des aspects intéroceptifs et affectifs, aux processus cognitifs de haut-niveau. Bien que la lexicologie soit variable pour aborder la question du self, la communauté scientifique s'accorde sur l'idée que le self peut être envisagé à différents niveaux, séparant le sujet de l'objet, au moment présent et de manière étendue dans le temps. L'étude comportementale du self et l'identification de ses réseaux cérébraux, représente un défi important, puisque ses différentes composantes sont fortement intriquées et difficilement dissociables. Les études semblent toutefois souligner une implication de l'insula, selon un axe de complexité postéro-antérieur, allant des basiques sensations corporelles et d'agentivité, aux capacités de métacognition et de conscience émotionnelle. L'implication de l'insula dans le self-conceptuel semble vraisemblable, bien que les rôles spécifiques de ses parties antérieure et postérieure restent à clarifier. Finalement, la contribution de l'insula dans la mémoire autobiographique est inconstante dans les études chez les sujets sains, mais pourrait être secondaire à son implication robuste dans le sens subjectif de soi, conférant un sentiment d'appartenance aux souvenirs personnels. Ces questions méritent d'être explorées de manière approfondie en essayant d'isoler les différentes composantes du self, pour en définir les réseaux cérébraux sous-jacents, notamment le rôle du cortex insulaire. En raison de son atteinte insulaire précoce, la MCL offre l'opportunité d'étudier le self et le lien qu'entretiennent ses différentes composantes.

OBJECTIFS & HYPOTHÈSES

3. Objectifs et hypothèses

Le self n'a jamais été étudié dans la MCL qui est pourtant la seconde maladie neuroévolutive, en termes de fréquence après la MA. Celle-ci a déjà largement servi de modèle d'étude pour le self, en particulier pour la mémoire autobiographique. La MCL est un modèle d'étude privilégié pour explorer le self, puisqu'elle se caractérise par une atteinte précoce de l'insula, qui semble occuper une place centrale dans les réseaux cérébraux des aspects les plus élémentaires du self. De plus, l'expérience clinique montre que la MCL est régulièrement associée à une anosognosie qui pourrait refléter des altérations du sens subjectif de soi, la composante la plus élémentaire du self, servant de prérequis à l'existence des trois autres, dans le modèle proposé par Prebble et collaborateurs (Prebble et al., 2013). Du point de vue clinique, l'étude du self dans la MCL permettrait de mieux comprendre les changements identitaires observés au cours de la maladie et les difficultés que les patients présentent pour accéder à leurs souvenirs, à la conscience de leurs troubles et à l'introspection de façon plus générale. Caractériser les atteintes du self dans cette population de patients pourrait offrir la possibilité de développer des programmes de remédiation cognitive centrés sur le self et ses aspects les plus élémentaires, afin d'agir sur ceux qui se trouvent en aval.

Le premier objectif de cette étude est de caractériser dans la MCL, l'altération des différentes composantes du self et les relations qu'elles entretiennent. Par l'analyse de données comportementales, nous souhaitons identifier les mécanismes cognitifs à l'œuvre, qui pourraient contribuer à l'effondrement identitaire, tel qu'il est perçu par l'entourage. Nous faisons l'hypothèse qu'il existe un effondrement global du self dans la MCL, avec une altération des composantes les plus élaborées telles que le self conceptuel et la mémoire autobiographique, secondairement à l'atteinte du sens subjectif de soi.

Le second objectif est de préciser le rôle de l'insula dans le sens subjectif de soi et d'identifier les substrats neuroanatomiques des autres composantes du self, telles que le self conceptuel et la mémoire autobiographique, par des analyses en imagerie volumétrique. Nous faisons l'hypothèse qu'il existe un lien entre la diminution du volume de matière grise dans l'insula, parmi d'autres régions impliquées dans les réseaux du self, et l'altération du sens subjectif de soi, du self conceptuel et de la mémoire autobiographique.

MÉTHODOLOGIE GÉNÉRALE

4. Méthodologie générale

Le projet SELF-MCL (N°IDRCB 2020-A02475-34) a été réalisé dans le cadre d'un travail de thèse, imaginé par le Pr Frédéric Blanc, le Dr Nathalie Philippi et moi-même, avec comme promoteur les Hôpitaux Universitaires de Strasbourg. En raison de l'épidémie de Covid19, le protocole n'a pu être approuvé par le comité d'éthique (CPP Sud Méditerranée III) qu'en janvier 2021, soit 10 mois après le début du contrat de doctorat. Cette recherche a fait l'objet d'un financement par l'association France Alzheimer, et la fondation Université de Strasbourg et Hôpitaux Universitaires de Strasbourg durant les trois premières années, puis par la fondation Vaincre Alzheimer pour la dernière année.

Avant d'aborder la partie expérimentale de ce travail, nous allons, dans un premier temps, présenter la cohorte de laquelle sont issus les sujets ayant participé à cette étude. Puis nous détaillerons les différents outils d'évaluation, tests et paradigmes, ayant permis de recueillir les données comportementales. Enfin, nous décrirons les différentes méthodes de traitement d'imagerie cérébrales utilisées à travers ces travaux de thèse.

4.1. Participants

4.1.1. Modalités de recrutement

Il s'agit d'une étude monocentrique non randomisée, en groupes parallèles, dans laquelle deux groupes de 20 participants ont été comparés : un groupe de patients atteints de MCL et un groupe de sujets témoins, appariés en âge, sexe et niveau socio-éducatif. L'inclusion des participants dans l'étude a été réalisée au Centre Mémoire de Ressources et de Recherche (CM2R) du Centre Hospitalier Universitaire de Strasbourg. Le recrutement a eu lieu sur les deux sites du CM2R : au sein de l'unité de neuropsychologie du service de neurologie, au CHU Hautepierre, et au sein l'hôpital de jour Saint-François du service de Gérontologie Mobile-Neuro-Psy-Recherche au CHU Robertsau. Les patients atteints de MCL étaient présélectionnés dans le cadre de leur suivi médical au CM2R. Les sujets témoins ont été sélectionnés par différents moyens : (i) parmi les proches des patients suivis au CM2R, (ii) parmi les sujets témoins du programme hospitalier de recherche clinique inter-régional (PHRC) « AlphaLewyMA » (http://clinicaltrials.gov/ct2/show/NCT01876459), (iii) à partir du fichier

des volontaires sains mis à disposition par le Centre d'Investigation Clinique (CIC) du CHU Hautepierre, (iv) via à une affiche de recrutement ayant été apposée dans les salles d'attentes du CM2R.

Pour être inclus dans l'étude, l'ensemble des participants devait remplir un certain nombre de critères. Ils devaient être un homme ou une femme, âgé de 60 à 85 ans au moment de la visite d'inclusion, affilié à un régime de protection sociale d'assurance maladie, bénéficiaire ou ayant-droit. Les sujets devaient être aptes à comprendre les objectifs et les risques liés à la recherche, et à donner un consentement éclairé, daté et signé. Ils devaient être droitiers, avoir une bonne maitrise de la langue française et avoir eu au minimum 9 années d'éducation formelle.

Pour le groupe de patients, les sujets devaient être au stade prodromal ou léger de la MCL, avec un score ≥ 20/30 au *mini-mental state examination* (MMSE) (Folstein et al., 1975). Les diagnostics de MCL et de MCL prodromique étaient basés sur les critères cliniques de McKeith (McKeith et al., 2017, 2020) (cf. § 2.3.1.). Certains des patients ont bénéficié d'analyses des biomarqueurs durant leur suivi clinique ; un DaTSCAN était réalisé lorsque le syndrome Parkinsonien était douteux et une analyse du LCS était réalisée devant un syndrome d'amnésie hippocampique suggérant une possible MA, afin d'éliminer une possible copathologie. Les patients avec une MCL prodromique étaient définis comme tel s'ils remplissaient les critères de McKeith pour le diagnostic de MCL au stade prodromal (McKeith et al., 2020), de trouble neurocognitif léger selon le DSM 5 (American Psychiatric Association & American Psychiatric Association, 2013), si leur autonomie dans les activités instrumentales de la vie quotidienne était préservée (Lawton & Brody, 1969) et s'ils présentaient un score ≥ 26/30 au MMSE (Folstein et al., 1975). Les patients avec une MCL au stade léger étaient définis comme tel s'ils remplissaient les critères de probable MCL selon les critères de McKeith pour le diagnostic de MCL (McKeith et al., 2017), si leur autonomie dans les activités instrumentales de la vie quotidienne était impactée (Lawton & Brody, 1969) et s'ils présentaient un score entre 20 et 25/30 au MMSE (Folstein et al., 1975).

Les sujets n'étaient pas inclus dans l'étude s'ils présentaient des comorbidités neuropsychiatriques significatives (e.g. maladie vasculaire avec un score de Fazekas >2, score Hachinski >7 ou antécédents d'AVC, de traumatisme crânien sévère, syndrome dépressif caractérisé, symptômes psychotiques non contrôlés), s'ils avaient des antécédents ou une

consommation actuelle excessive et régulière d'alcool (> 2 unités par jour), s'ils présentaient un handicap sensoriel pouvant interférer significativement avec les évaluations comportementales (e.g. surdité sévère, trouble visuel sévère), s'ils présentaient une anomalie à l'examen neurologique (à l'exception d'un syndrome Parkinsonien chez les patients atteints de MCL), s'ils suivaient un traitement médicamenteux psychotrope lourd, selon le jugement de l'investigateur (e.g. clozapine > 25 mg / jour), s'ils étaient claustrophobes ou s'ils présentaient une contre-indication à l'IRM (e.g. porteur d'un pacemaker, d'une pompe à insuline, d'un clip vasculaire, d'éclat métallique intraoculaire, de prothèse métallique), s'ils se trouvaient en période d'exclusion (déterminée par une étude précédente, ou en cours), ou s'ils étaient sous sauvegarde de justice, sous tutelle ou sous curatelle. Les patients dont l'analyse du LCS révélait des biomarqueurs en faveur d'une MA (i.e. ratio Aβ42/Aβ40 anormal, augmentation de t-Tau et phospho-Tau181) n'étaient pas inclus dans l'étude. Les sujets témoins qui présentaient une plainte cognitive, ou dont l'autonomie dans les activités instrumentales de la vie quotidienne était impactée, n'étaient pas inclus dans l'étude.

4.1.2. Déroulement pratique du protocole

L'inclusion des participants à l'étude SELF-MCL s'est déroulée entre janvier 2021 et février 2023. Après avoir reçu des informations détaillées sur l'étude de manière orale et par écrit, les participants bénéficiaient d'un délai de réflexion d'au moins 48h, en amont du recueil de consentement. Leur participation au protocole s'étendait ensuite sur quatre demi-journées, réparties sur une période entre deux à 12 semaines. La chronologie des visites et leur contenu est illustré par la figure 6.

La visite d'inclusion était réalisée au CM2R : soit à l'unité de Neuropsychologie du CHU Hautepierre, soit à l'hôpital de jour gérontologique Saint François du CHU Robertsau. Les patients étaient accompagnés d'un proche. Après avoir répondu aux éventuelles questions, un médecin investigateur était chargé de recueillir le consentement libre, éclairé et écrit du patient et de son proche. Au cours de cette visite, un premier entretien avec le médecin investigateur permettait de recueillir les antécédents médicaux et traitements concomitants, d'effectuer un examen clinique avec une mesure des paramètres vitaux et un examen neurologique, ainsi que l'évaluation de différents aspects cognitifs et comportementaux. Une

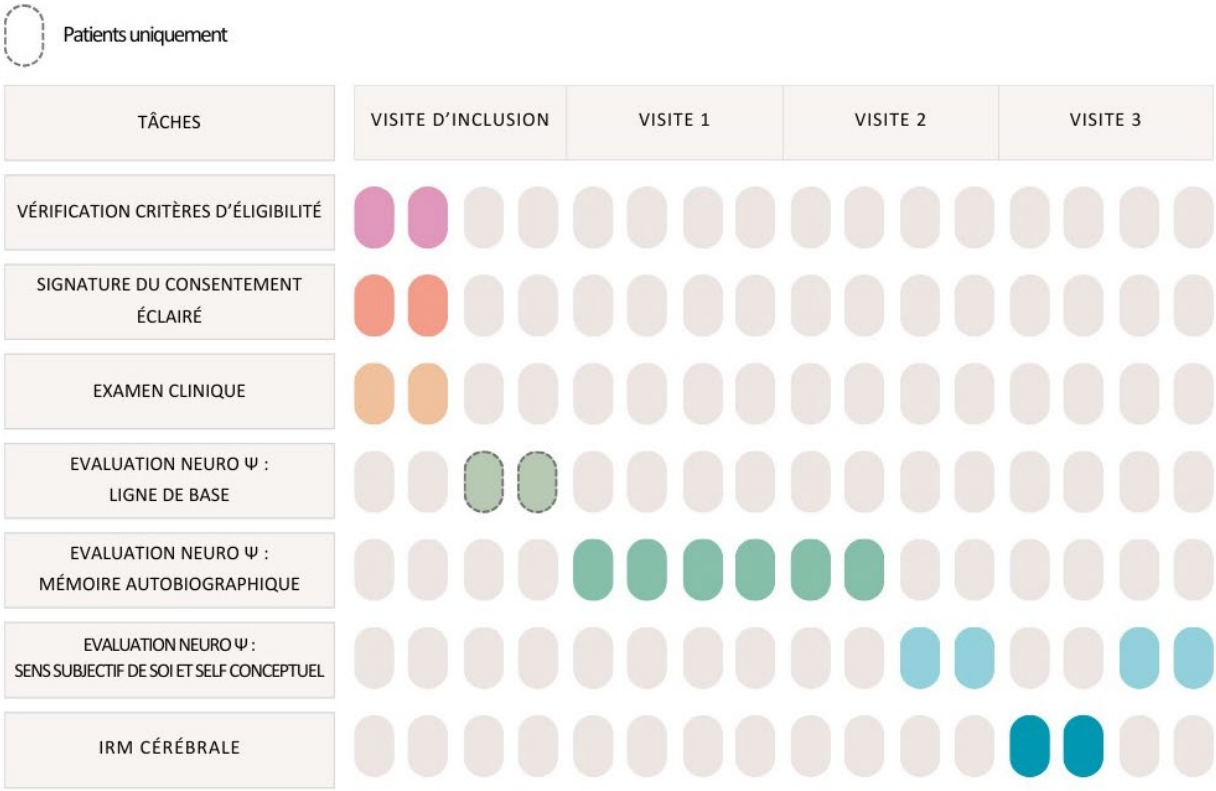

Figure 6 *Chronologie et contenu des visites du protocole SELF-MCL, visant à étudier le self et ses bases neuronales dans la maladie à corps de Lewy. Ψ Psychologique, IRM imagerie par résonnance magnétique*

évaluation neuropsychologique classique était ensuite administrée en ligne de base, pour les patients uniquement.

Les visites 1 et 2 avaient lieu dans les locaux du CM2R, ou à domicile, lors de la periode de Covid-19 qui imposait une restriction des sorties. La visite 1 comprenait une évaluation neuropsychologique spécifique de la mémoire autobiographique pour l'ensemble des participants. La première partie de la visite 2 était consacrée à la poursuite de l'évaluation de la mémoire autobiographique, alors que la deuxième partie permettait d'évaluer le sens subjectif de soi et le self conceptuel.

La visite 3 avait lieu à l'Institut de Physique Biologique sur le campus de l'hôpital civil, et comprenait la passation d'une IRM cérébrale multimodale, suivie d'une évaluation du sens subjectif de soi.

4.2. Description des outils d'évaluation comportementale

Les outils utilisés pour recueillir les données comportementales sont décrit dans la présente section.

4.2.1. Ligne de base neuropsychologique

Les capacités cognitives générales telles que la mémoire antérograde verbale (RLRI16, Grober et al., 1988), les fonctions exécutives (Fluences phonologiques et sémantiques, Thurstone & Thurstone, 1964; Batterie Rapide d'Efficience Frontale (BREF), Dubois et al., 2000 ; Trail Making Test B, « Army Individual Test Battery », 1944; Goul & Brown, 1970), les mémoires à court terme et de travail auditivo-verbales (mémoire des chiffres, Wechsler, 1997), la vitesse de traitement de l'information (Trail Making Test A, « Army Individual Test Battery », 1944; Goul & Brown, 1970) et les capacités visuoconstructives (Figure complexe de Rey-Osterrieth, Rey, 1941) ont été évaluées chez les patients, en plus de l'évaluation spécifique des composantes du self.

4.2.2. Evaluation du self

4.2.2.1. Sens subjectif de soi

Le sens subjectif de soi est une composante primaire particulièrement difficile à isoler et, par conséquent, à évaluer. Cependant, il est possible de l'étudier par les capacités intéroceptives (Craig, 2002), dont la mesure d'évaluation la plus courante repose sur la détection des battements cardiaques (Brener & Ring, 2016, 2016; Schandry, 1981).

Ainsi, dans cette étude, une tâche de détection des battements cardiaques (HTT) permettait de mesurer les capacités intéroceptives des sujets, en évaluant la différence entre les battements cardiaques ressentis par les individus (mesure subjective) et mesurés par un examinateur (mesure objective) (Garfinkel et al., 2015). Les participants étaient installés en décubitus dorsal, les bras le long du corps. Il leur était demandé de fermer leurs yeux et d'essayer de percevoir les battements cardiaques dans leur poitrine, sans mesurer leur pouls. Lorsqu'ils parvenaient à ressentir leurs battements cardiaques, ils devaient le signaler à l'examinateur, qui donnait ensuite un signal de départ à partir duquel les participants devaient commencer à compter silencieusement leurs battements cardiaques durant 20 secondes. Simultanément, l'examinateur mesurait le pouls sur leur poignet gauche. Lorsque l'examinateur donnait le signal d'arrêt, les participants devaient rapporter le nombre de battements cardiaques ressenti durant l'essai. La tâche était répétée trois fois, de manière à

augmenter la quantité de matériel à analyser. Les mesures subjectives étaient ensuite confrontées aux mesures objectives, permettant d'obtenir un score de précision.

Nous avons également évalué le sens subjectif de soi dans ses différentes composantes par d'autres moyens :

- Dans sa composante préréflexive, par une tâche d' « agentivité » informatisée, élaborée par notre équipe, et par l'Échelle du Sens d'Agentivité adaptée (Tapal et al., 2017).
- Dans sa composante métacognitive par un questionnaire sur le contenu de la pensée élaboré par notre équipe et qui était complété à l'issue de la séquence d'IRM fonctionnelle (cf. § 4.3.).
- Dans sa composante métacognitive par un questionnaire d'anosognosie, adapté de L'« *Anosognosia Questionnaire-Dementia »* de Starkstein et collaborateurs (Starkstein, 2006).

Les résultats de ces évaluations feront l'objet de prochains articles, mais ne seront pas présentés dans le présent manuscrit.

4.2.2.2. Self conceptuel

Le self conceptuel a été évalué par le Twenty Statements Test (TST, Kuhn & McPartland, 1954). Il était demandé aux participants de produire, par écrit, jusqu'à 20 affirmations répondant à la question « qui suis-je ? », en complétant la phrase « Je suis… ». Des indices sur les différentes catégories de réponses possibles parmi les cinq domaines de l'identité (physique, personnel, familial, social, moral) étaient proposés, ainsi que des exemples correspondant à chaque catégorie, afin de limiter un éventuel déficit d'initiation. Les instructions et indices apparaissaient sur la feuille de réponse.

Dans notre étude, nous nous sommes intéressés au nombre de réponses produites par les participants, sans tenir compte des différentes catégories. Les réponses répétitives ou qui ne répondaient pas à la question d'intérêt n'étaient pas prises en compte.

Nous avons également évalué le self-conceptuel par :

- Un questionnaire sur les changements de goûts que notre équipe a élaboré, et précédemment utilisé dans des études préliminaires (Philippi et al., 2020).
- L'échelle IOWA (Juillerat et al., 1998), complétée par l'aidant qui visait à mesurer les changements de personnalité.

Les résultats de ces évaluations feront l'objet de prochains articles, mais ne seront pas présentés dans le présent manuscrit.

4.2.2.3. Mémoire autobiographique

La mémoire autobiographique a été évaluée par l'Autobiographical Interview (AI; Levine et al., 2002). Il était demandé aux participants de rappeler des souvenirs d'évènements personnels à travers cinq périodes de vie (0-15 ans, 15 à 30 ans, 30 à 50 ans, 50 à [l'âge actuel – 1], au cours de l'année précédente). Dans la version classique de l'AI, seul un épisode par période de vie est recueilli. Dans notre étude, les participants devaient rappeler, dans la mesure du possible, deux souvenirs par période de vie, de manière à augmenter la quantité de matériel à analyser. Pour les aider à se remémorer des souvenirs, les participants se sont vu proposer une liste de 20 mots « indices » (e.g. piano, pomme, bateau), néanmoins, les souvenirs sans rapport avec les mots indices étaient également pris en compte.

Pour analyser les effets facilitateurs du support de récupération sur la mémoire, nous avons manipulé le niveau de structure des souvenirs selon trois conditions : rappel libre, indiçage général et indiçage spécifique. Lors du rappel libre, les participants racontaient l'évènement sans interruption de la part de l'examinateur, jusqu'à ce qu'ils arrivent naturellement à la fin de leur histoire. À la fin du récit du participant, l'examinateur l'invitait, une unique fois, à rappeler davantage de détails (indiçage général). Enfin, la phase d'indiçage spécifique consistait en un entretien structuré visant à recueillir des détails selon quatre domaines : temporel, spatial, perceptuel, émotionnel/pensée.

Les récits des participants étaient enregistrés à l'aide d'un dictaphone numérique et retranscrits verbatim. Les souvenirs étaient ensuite analysés selon un système de cotation complexe, destiné à rendre compte du niveau de détail de façon quantitative et à classer les souvenirs selon leur spécificité. Pour ce faire, la description des événements était segmentée en détail. Chaque détail était ensuite classifié comme « interne » ou « externe » à

l'événement. Le détail était considéré comme « interne » puis associé à l'une des cinq catégories (détail événementiel, temporel, spatial, perceptuel, émotionnel/pensée) s'il s'agissait d'un détail directement lié à l'événement principal, spécifique au moment et au lieu, générant un sentiment de reviviscence. Le détail était considéré comme « externe » s'il s'agissait d'un événement autobiographique satellite, ou s'il s'agissait d'un détail n'étant pas lié à l'événement principal, d'un fait sémantique, d'un fait déjà évoqué précédemment (répétition), ou encore d'un détail de type métacognitif.

Les détails de chaque catégorie étaient ensuite additionnés séparément, pour chaque condition (i.e. rappel libre, indiçage général, indiçage spécifique). Étant donné que l'effet de l'indiçage général est minime comparé à celui de l'indiçage spécifique (Levine et al., 2002), les scores de rappel libre et d'indiçage général étaient combinés. Les scores quantitatifs étaient ensuite convertis en scores qualitatifs pour les domaines temporel, spatial, perceptuel, émotionnel/pensée, avec un score qualitatif maximal de trois pour chaque domaine. Un score de trois points était attribué lorsque la description était riche, hautement spécifique et semblant émaner d'un sentiment de reviviscence. Un score de deux points était attribué à une description détaillée, mais n'étant pas suffisamment riche pour bénéficier de trois points. Un score d'un point était attribué à une description générale, ne contenant pas d'information spécifique, mais tout de même de nature épisodique. Un score de zéro point était attribué lorsqu'il n'y avait aucune information relative au domaine spécifique, ou pour des réponses basées sur des connaissances sémantiques, plutôt que sur la mémoire épisodique. La richesse épisodique (i.e. niveau de reviviscence général transmis à travers le récit) était cotée sur une échelle similaire en six points, d'une part afin d'améliorer la précision de l'évaluation, et d'autre part pour augmenter la valeur de ce paramètre, comparativement aux autres domaines. Bien que les scores des quatre premiers domaines s'exclussent mutuellement (i.e. les aspects d'un souvenir, ne pouvaient pas être considérés dans plus d'une catégorie), la richesse épisodique était basée sur l'évaluation globale de l'événement, en tenant compte des scores attribués aux quatre domaines susmentionnés. Afin d'étudier les éventuelles différences selon la période de vie, les scores de richesse épisodique des deux souvenirs étaient additionnés pour chaque période, pour le rappel libre (i.e. rappel libre plus indiçage général) et pour le rappel avec indiçage spécifique (i.e. score total après l'indiçage spécifique) (score maximal = 36). Afin d'analyser les éventuelles différences entre les deux conditions de

rappel, les scores totaux de chaque période étaient additionnés afin d'obtenir un score général de rappel libre et un score général de rappel avec indiçage spécifique (score maximal = 180).

La cotation des souvenirs a été réalisée par un examinateur formé (Alice Tisserand). Afin d'évaluer la fiabilité interexaminateurs, 10% des souvenirs ont été sélectionnés au hasard (avec la contrainte que l'âge, les groupes et les périodes de vie soient équitablement représentés) et cotés par un autre examinateur formé (Nathalie Philippi), qui ne connaissait pas le statut du sujet, conformément aux procédures de cotation établies dans d'autres études (Levine et al., 2002, p. 200; Verfaellie et al., 2014).

La mémoire autobiographique a également été évaluée par :

- Les Self Defining Memories (Blagov & Singer, 2004) qui visaient à recueillir cinq souvenirs marquants.
- Un questionnaire de sémantique personnelle élaboré par notre équipe et inspiré de l'Autobiographical Memory Interview (Kopelman et al., 1989).

Les résultats de ces évaluations feront l'objet de prochains articles, mais ne seront pas présentés dans le présent manuscrit.

4.3. Analyses de neuroimagerie

Dans le cadre de cette étude, les données d'imagerie ont été acquises sur un appareil SIEMENS 3T VERIO (Siemens, Erlangen, Allemagne) équipé d'une antenne réceptrice tête à 32 canaux. L'examen durait 51 minutes au total, et comprenait les séquences suivantes : FLAIR 3D, T1 3D, Diffusion, ASL, SWI, BOLD.

Dans notre étude, les bases neurales du self ont pu être étudiées du point de vue anatomique, à travers des analyses d'imagerie volumétrique, ou de « *morphométrie structurelle* ».

4.3.1. La « Voxel-Based Morphometry » (VBM)

La VBM est une technique permettant de caractériser le volume cérébral régional à partir d'images anatomiques pondérées en T1. Dans notre étude, un contrôle de qualité de ces

images était tout d'abord effectué, afin de contrôler d'éventuels artefacts. Les analyses en VBM comprenaient ensuite différentes étapes : une phase de prétraitement et une phase d'analyses statistiques. Ces étapes étaient réalisées par le logiciel SPM12 (Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/), à partir du logiciel Matlab R2017b (MathWorks, Natick, MA, USA).

Le prétraitement des images suivait la procédure standard (Good et al., 2001). Les images anatomiques pondérées en T1 étaient tout d'abord segmentées en six classes de tissus (matière grise, substance blanche, LCS, os, tissus mous, air) et une correction des biais d'intensité était appliquée (Ashburner & Friston, 2005). Les images étaient ensuite normalisées vers l'espace du *Montreal Neurological Institute* (MNI) avec l'approche DARTEL. Une étape de modulation permettait ensuite de préserver la quantité totale de matière grise présente dans les données d'origine, en ajustant l'intensité de chaque voxel en fonction de la déformation appliquée lors de la normalisation. Enfin, l'étape de lissage consistait à appliquer sur les images un noyau gaussien isotrope (*full width at hald maximum* [FWHM] 8mm) permettant d'augmenter le rapport signal/bruit.

Les analyses statistiques ont ensuite été effectuées à l'aide de modèles linéaires généralisés, pour permettre d'établir des comparaisons intergroupes du volume de matière grise entre les patients atteins de MCL et les sujets témoins, et pour identifier les régions cérébrales impliquées dans les différentes composantes du self, par des corrélations volumétriques au sein du groupe MCL.

LE SELF DANS LA MALADIE À CORPS DE LEWY : PARTIE EXPÉRIMENTALE

PARTIE EXPÉRIMENTALE : LE SELF DANS LA MALADIE À CORPS DE LEWY

Dans cette section, nous commencerons par présenter les caractéristiques générales de notre cohorte de sujets. Nous présenterons ensuite notre étude sur le sens subjectif de soi, suivie de l'étude sur le self-conceptuel, et de l'étude sur la mémoire autobiographique, dans la MCL. Enfin, nous terminerons par un chapitre sur le lien entre les différentes composantes du self.

1. Description des échantillons

1.1. Caractéristiques démographiques

Au total, 20 patients atteints de MCL prodromique à légère et 21 sujets témoins appariés en âge, sexe, et niveau socio-éducatif (avec un minimum de 9 années d'éducation formelle) ont été inclus dans l'étude. Un des sujets témoins est décédé en cours d'étude – un décès sans lien avec les procédures expérimentales – et les analyses ont donc été effectuées exclusivement sur 20 sujets témoins. Le tableau 2 résume les caractéristiques démographiques de la population. Le groupe de patients MCL comprenait 14 hommes et 6 femmes, entre 60 et 85 ans (μ = 71,9, σ = 7,9), dont 13 patients atteints de MCL prodromique et 7 patients atteints de MCL au stade léger. Le groupe de sujets témoins était apparié en âge (*P* = .597), sexe (*P* = .507), années d'éducation (*P* = .096) et latéralité manuelle (*P* = .311).

Tableau 2 *Caractéristiques démographiques des patients atteints de MCL et des sujets témoins*

CARACTÉRISTIQUES	PATIENTS MCL (N=20)	SUJETS TÉMOINS (N=20)	*t* DE STUDENT / $\chi 2$
Âge	71.9 (7.9)	70.6 (7.4)	*t* = 0.53, *P* = .597
Sexe, M/F	14/6	12/8	$\chi 2$ = 0.44, *P* = .507
Années d'éducation	12.7 (2.5)	14.2 (2.8)	t = -1.705, P = .096
Latéralité, G/D	19/1	20/0	$\chi 2$ =1.03, *P* = 0.311
Score MMSE (/30)	26.3 (2.39)	28.9 (1)	t = -4.32, P < .001

MMSE Mini-Mental State Examination.

1.2. Caractéristiques sémiologiques

Les principales caractéristiques sémiologiques de l'échantillon de patients sont résumées dans le tableau 3. De manière très fréquente, il existait des fluctuations (85%), alors que les hallucinations/illusions et troubles du comportement en sommeil paradoxal concernaient un peu plus de la moitié du groupe de patients (60% pour chacun des paramètres). Les patients présentaient tous un syndrome extrapyramidal, caractérisé par la présence d'au moins un signe (akinésie, rigidité musculaire, tremblement). L'akinésie était le signe extrapyramidal retrouvé le plus fréquemment (80%), suivi de près par la rigidité musculaire (70%). Seul un patient présentait un tremblement de repos. Les troubles dysautonomiques étaient très fréquents dans notre échantillon (95%). La manifestation dysautonomique la plus fréquente était des troubles sphinctériens (70%), une augmentation des sécrétions concernait également plus de la moitié de l'échantillon (65%), un syndrome sec et des troubles neurosensoriels concernaient la moitié de l'échantillon.

Tableau 3 *Caractéristiques sémiologiques des patients atteints de MCL*

CARACTÉRISTIQUES SÉMIOLOGIQUES	PATIENTS MCL (N = 20)
Fluctuations (%)	17/20 (85)
Hallucinations/illusions (%)	12/20 (60)
TCSP (%)	12/20 (60)
Syndrome extrapyramidal (%)	20/20 (100)
Akinésie (%)	16/20 (80)
Rigidité musculaire (%)	14/20 (70)
Tremblement de repos (%)	1/20 (5)
Dysautonomie	19/20 (95)
Syndrome sec (Sècheresse buccale, oculaire, nasale) (%)	10/20 (50)
Augmentation des sécrétions (hypersalivation, rhinorrhées, lacrimation) (%)	13/20 (65)
Troubles sphinctériens (troubles urinaires/constipations) (%)	14/20 (70)
Troubles neurosensoriels (troubles du goût, de l'odorat, photophobie) (%)	10/20 (50)

1.3. Marqueurs biologiques

Le tableau 3 présente les marqueurs biologiques des patients qui en ont bénéficié durant leur suivi clinique. Au total, 13 patients avaient bénéficié d'une analyse du LCS avec dosages des biomarqueurs neurodégénératifs. Trois ponctions lombaires étaient pathologiques, dont une qui présentait une diminution isolée de l'Aβ42 et deux qui présentaient une augmentation des protéines T-tau et P-tau, mais avec un ratio Aβ42/40 normal dans tous les cas. Sept patients avaient bénéficié d'un DaTSCAN, dont la réalisation était principalement motivée par un syndrome extrapyramidal discret. Six d'entre eux présentaient un DaTSCAN pathologique, contre un normal.

Tableau 4 *Marqueurs biologiques chez les patients atteints de MCL ayant bénéficié d'une analyse du LCS ou d'un DaTSCAN durant leur suivi clinique*

MARQUEURS BIOLOGIQUES	PATIENTS MCL
Biomarqueurs du LCS (N = 13)	
↓ Peptide Aβ42	1/13
↑ Protéine T-tau	2/13
↑ Protéine P-tau	2/13
DaTSCAN (N = 7)	
Positif	6/7
Négatif	1/7

LCS Liquide cérébrospinal.

1.4. Ligne de base neuropsychologique

Afin de caractériser les déficits neuropsychologiques des patients atteints de MCL, une batterie de tests évaluant l'ensemble des fonctions cognitives leur était administrée. Les résultats sont présentés dans le tableau 5.

Tableau 5 *Ligne de base neuropsychologique chez les patients atteints de MCL*

PATIENT	RLRI 16			FLUENCES		BREF	EMPANS	TMT A		TMT B		FCR
	Encodage	*RDL*	*RDT*	*Sémantique*	*Phonologique*		*NS*	*Temps*	*Erreurs*	*Temps*	*Erreurs*	*Score*
1	14*	6*	16	11*	6*	10*	12	186*	2*	203*	3*	29
2	15	11	16	24	11*	12*	11	90	1*			8*
3	15	0*	4*	15*	13*	13*	12	45	0	179*	1	33.5
4	16	12	16	36	27	17	12	46	0	58	0	36
5	15	6*	12*	19	8*	12*	10	48	0	277*	0	9.5*
6	14*	15	16	16*	12*	n/a	6*	104*	0	216*	0	33
7	7*	5*	10*	20	17	11*	5*	68	0			33
8	10*	2*	6*	23	22	15*	9	54	0	210*	0	
9	14*	9	15	20	14	16*	5*	41	0	58	1	35
10	16	9*	15	30	20	18	11					34
11	14*	6*	10*	25	28	16*	11	84*	1*	116	1*	31
12	14*	12	15	23	17	18	10	47	0	115	0	33
13	14*	11	16	26	26	14*	15	54	0	121	3	33
14	11*	0*	10*	23	2*	10*	8	50	0	122	1	30
15	13*	1*	11*	18*	17	9*	9	133*	0			10*
16	12*	9*	15	25	25	17	7*	55	0	160*	1*	32
17	14*	9*	15	18*	25	16*	15	27	0	55	0	29
18	12*	n/a	n/a	11*	11*	12*	14	96	0			21*
19	15	6*	13*	16	22	16*	12	63	0	81	0	36
20	10*	3*	5*	11*	22	16*	8	90*	1*			29
Moyenne	13.25	6.95	12.42	20.50	17.25	14.11	10.10	72.68	0.26	140.79	0.79	28.16
ET	2.29	4.38	3.98	6.44	7.48	2.88	2.99	38.16	0.56	68.71	1.05	9.10

RDL Rappel différé libre ; RTL Rappel différé total ; BREF Batterie Rapide d'Efficience Frontale ; TMT Trail Making Test ; FCR Figure complexe de Rey-Osterrieth. Les données étaient disponibles au RLRI16 encodage pour 20 patients, aux rappels différés libre et indicé pour 19 patients, aux fluences phonologiques et sémantiques pour 20 patients, au TMT B pour 14 patients, à la BREF pour 19 patients, au TMT A pour 19 patients, aux empans endroit et envers pour 20 patients, à la figure de Rey pour 19 patients. Les scores marqués d'une étoile représentent les scores déficitaires selon les données normatives des différents tests.

1.5. Imagerie volumétrique

L'analyse en VBM comparant les patients atteints de MCL aux sujets témoins est présentée dans la figure 7. Il existait une diminution de matière grise dans les régions insulaires, temporales, occipitales, frontales, cingulaires, et dans une moindre mesure dans les régions pariétales, chez les patients atteints de MCL comparé aux sujets témoins, en incluant le volume total intracrânien et l'âge comme covariables de nuisance (P <.05, corrigé en FDR).

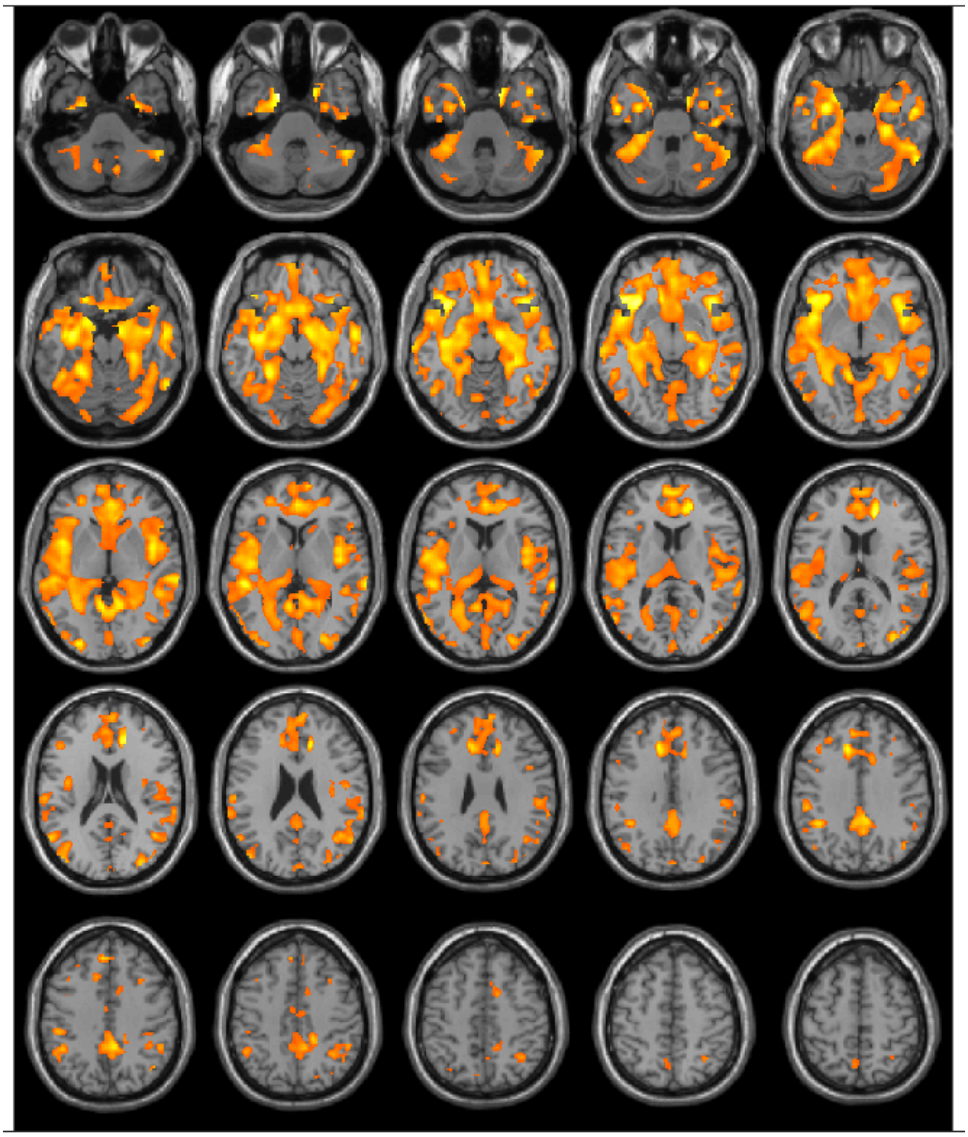

Figure 7 *Analyses volumétrique comparant les patients atteints de maladie à corps de Lewy aux sujets témoins* (*P* < 0.05, corrigé en FDR)

2. Étude du sens subjectif de soi dans la MCL

« Je sens, donc je suis » : l'intéroception comme mesure du sens subjectif de soi, étude comportementale

Cette première étude a permis d'explorer le sens subjectif de soi, qui est la composante la plus élémentaire du self, sur laquelle reposeraient le self-conceptuel et de la mémoire autobiographique, selon le modèle de Prebble et collaborateurs (Prebble et al., 2013). Le sens subjectif de soi distingue deux sous-composantes hiérarchisées (Prebble et al., 2013). La première, l'expérience « préréflexive » fait référence à un flux d'expériences perceptuelles, de pensées et à l'agentivité. La deuxième que l'on désigne par le terme de « self-awareness », qui ne connait pas d'équivalent en français, fait référence à un niveau de conscience réflexive, impliquant une analyse métacognitive, au cours de laquelle le sujet devient également l'objet de la conscience (e.g. « je n'arrête pas de me perdre, j'ai des problèmes d'orientation »).
La présente étude s'est intéressée à l'analyse de l'expérience préreflexive, dont l'évaluation comportementale n'est pas aisée en raison de son caractère élémentaire. Il existe toutefois des paradigmes complexes permettant d'évaluer l'expérience préreflexive, tels que le paradigme de « l'illusion de la main étrangère », qui vise à isoler le sens d' « ownership » (Tsakiris et al., 2007), ou encore des questionnaires d'agentivité, qui peuvent néanmoins s'avérer difficiles à comprendre pour les patients. Une autre approche de l'expérience préreflexive consiste à étudier l'intéroception, dont l'insula est une région centrale (Craig, 2002). Dans cette étude, nous avons évalué l'intéroception aux moyens d'une tâche, finalement simpliste de détection des battements cardiaques en trois essais (Schandry, 1981). La « sensibilité intéroceptive » était calculée sur la base de la différence entre le nombre de battements perçus par le sujet et le nombre de battements objectifs, tel que mesuré par l'examinateur. La moyenne des scores d'erreur sur les trois essais était ensuite comparée entre les patients atteints de MCL et les sujets témoins. Nous nous sommes également intéressés aux différences de volumétrie cérébrale dans l'insula, entre les patients présentant une préservation relative des capacités intéroceptives et les patients présentant un déficit plus sévère des capacités intéroceptives.
Étant donné qu'il existe une atteinte précoce de l'insula dans la MCL (Roquet et al., 2017), et que l'insula tient un rôle central dans l'intéroception (Craig, 2002), nous avons fait l'hypothèse

d’une altération de la capacité à détecter les battements cardiaques chez les patients atteints de MCL, suggérant une atteinte du sens subjectif de soi, en lien avec l’atrophie insulaire.

"I feel therefore I am" : interoception as a way to assess the subjective sense of self in dementia with Lewy bodies, an exploratory study

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Abstract

Dementia with Lewy bodies (DLB) is characterized by early insular atrophy. The insula is known to be a core region of interoception, which is part of self, precisely the prereflective aspects of the subjective sense of self (SSS). It is the most basic component of the self that would support the most elaborated ones, such as the self-concept and autobiographical memory, which we have recently shown to be impaired in prodromal DLB. The purpose of this study was to investigate the SSS and to identify its neuroanatomical correlates in prodromal DLB, hypothesizing that interoception would be altered in relation to insular atrophy. Twenty patients with prodromal to mild DLB and 20 matched healthy controls were enrolled in the study. We used a heartbeat tracking task to evaluate interoceptive accuracy. Behavioral performances were compared between patients and control subjects. Three-dimensional magnetic resonance images were acquired for all participants and voxel-based morphometry was used to investigate the differences in cortical volumes, in patients with severe interoceptive disorders and patients with mild or no interoceptive disorders, compared to

control subjects. The behavioral results confirm the existence of prereflective SSS impairments in DLB patients, compared to matched healthy controls. Moreover, as we expected, neuroimaging analyses revealed greater insular atrophy in patients with severe interoceptive deficits, among other structures involved in the SSS processes, compared to patients with mild or no interoceptive disorders. These findings suggest that prereflective SSS impairments in DLB could be related to insular atrophy and could be at the origin of a global collapse of the self in the disease.

Keywords : Dementia with Lewy bodies, self, subjective sense of self, interoception, insula

Introduction

Everyone has already experienced a feeling of fullness after a good meal, nausea in a disgusting situation or palpitations in a stressful situation. Generated by emotions (Damasio, 1993) as well as physiological needs, these bodily sensations are what we call interoception. Interoception, or the sense of physiological condition of the body, is part of the subjective sense of self (SSS), which is an essentially human characteristic that provides one with the feelings of singularity, coherence, individuality and unity (Prebble et al., 2013). In Prebble' theoretical self model, the SSS is a crucial precondition for the other more elaborated components of the self to exist, such as the self-concept and episodic autobiographical memory (Prebble et al., 2013; Tulving, 1985). Little work has investigated the neural basis of the SSS, but there seems to be a clear connection with the insular cortex (Farrer et al., 2003; Frewen et al., 2020; Seth, 2013; Tsakiris et al., 2007), particularly in interoceptive capacities (Craig, 2002, 2009). We were therefore interested in the SSS in dementia with Lewy bodies (DLB), which is characterized by early insular atrophy (Blanc et al., 2015; Roquet et al., 2017).

The SSS is made up of two hierarchically related forms of present-moment conscious experience: the prereflective self-experience and self-awareness. Prereflective experience involves a sense of body ownership that confers the feeling that "I" am the one undergoing an experience (Gallagher, 2000), which is *de facto* essential for encoding, storing and consolidating this experience in memory. The prereflective experience also involves a sense of agency which confers the feeling that "I" am the one causing of generating an action and its effect (Gallagher, 2000). Bodily awareness refers to the conscious perception of somatic and internal sensations and to awareness that these experiences are bound to the self (Berlucchi & Aglioti, 2010; Blanke, 2012; Blanke et al., 2015; Legrand, 2006, 2010). It is a multidimensional construct that involved the feeling of owning a body and being the agent over one's own actions (Berlucchi & Aglioti, 2010; Blanke, 2012; Blanke et al., 2015). The second component

of the SSS, self-awareness, represents a higher and reflective level of awareness reflecting the ability to introspect about one's mental states, behavior and experiences (Keenan et al., 2005; Leary & Tangney, 2012; Stuss & Levine, 2002). The SSS, and especially the prereflective experience represents a real challenge to evaluate. However, one way to measure it consists of assessing interoception, which refers to the central processing and representation of internal bodily signals. The interoceptive sensations arising from the body allows for a continuous monitoring of the state of the body through mechanisms, such as heart rate, blood pressure, respiration, proprioceptive signals and visceral activity (Craig, 2008, 2010). Interoception contributes to the evaluation of whether a change is from the inside or from the outside of the body, and therefore allows to distinguish the "self" from the "non-self". Craig's work on the anatomy of interoceptive processes indicates a central role for the insula (Craig, 2002), with a posterior-to-mid-anterior pattern of integration of interoceptive information (Craig, 2009). The primary interoceptive representations would be located in the posterior part of the insula and re-represented in an integrative zone in the mid-insula, and again in the anterior insular cortex, making the information available for awareness (Brooks et al., 2002; Craig et al., 2000; Olausson et al., 2002, 2005). Interestingly, by means of a heartbeat tracking task (HTT), previous evidence found interoceptive impairments related to atrophy in the insular cortex, the anterior cingulate cortex (ACC) and the frontal lobe in neurodegenerative diseases including Alzheimer's disease (AD), behavioral variant frontotemporal dementia (bvFTD) and Parkinson's disease (PD) (Garcia-Cordero et al., 2016; Salamone et al., 2021). A single case study on a patient with bvFTD also suggests involvement of the insulae, the postcentral gyrus and the orbitofrontal cortex in interoception and food aversion (Salvato et al., 2018). Moreover, in a meta-analysis involving patients with anxiety and mood disorders, authors found a role for the posterior insular cortex in a HTT, suggesting that the anterior

insular cortex may rather be concerned with evaluative aspects of interoception (Schulz, 2016). The HTT consists of measuring the accuracy on perceiving and counting heartbeats during a period (Schandry, 1981). Thus, individuals accurately counting the beats of the heart are considered as having higher interoceptive accuracy. Cardiac interoceptive tests like the HTT are widely used measures to assess interoception, although the psychometric limitations of these tasks are well described (Brener & Ring, 2016), as it is difficult to collect objective evidence of interoception and to control it experimentally. However, a recent study showed that HTT has high reliability and that reducing the number of blocks in the task did not impact HTT outcomes (Santos et al., 2022).

Recently, we found impairments of the more elaborated components of the self in the same sample of DLB patients as in the present study. Indeed, we demonstrated deficits of the self-concept and autobiographical memory, which were partly related to insular atrophy (Philippi et al., 2020; Tisserand et al., 2020, 2023, 2024). Thus, the aim of the present paper was to explore the SSS and its relationship with the insula, by thoroughly assessing interoceptive abilities with a HTT. Based on the assumption that insula plays a key role in interoception, we predicted that interoceptive abilities would be impaired in DLB patients, in relation to insular atrophy. We believe that insular damage would cause alterations of the SSS, that would lead to a global collapse of the self, whose most elaborated components such as the self-concept and autobiographical memory are grounded on the SSS.

Methods

Study population

Twenty patients with early-stage DLB and 20 healthy control subjects matched for age, gender, and level of education (with a minimum of 9 years) were enrolled in the present study between January 2021 and February 2023. Patients were recruited from the tertiary memory clinic of Strasbourg University Hospital (CM2R of Strasbourg), France, including the Geriatrics and Neurology Departments. Control subjects were recruited in three ways: among friends and relatives of the patients, via the listing of controls of the local clinical investigation centre and from the control group of the AlphaLewyMA cohort (http://clinicaltrials.gov/ct2/show/NCT01876459). Diagnosis of prodromal and mild DLB was based on core clinical features (I. McKeith et al., 2020; I. G. McKeith et al., 2017). Some of the patients had also benefited from biomarkers during their clinical follow-up. Indeed a dopamine transporter (DAT) imaging was performed when parkinsonism was doubtful, and a cerebrospinal fluid (CSF) analysis was performed when an amnestic syndrome of hippocampal type suggested possible Alzheimer's disease, to ensure that there was no co-pathology. Thus, a DAT scan was available to support the diagnosis in approximately a quarter of the patients, and CSF analysis was available to confirm the absence of associated Alzheimer's disease in approximately half of the patients. Patients with prodromal DLB were defined as having mild cognitive impairment if they had a Mini-Mental State Examination (MMSE) score ≥ 26, had preservation of independence as assessed by the Instrumental Activities of Daily Living (Lawton & Brody, 1969) and fulfilled both the DSM-5 criteria of mild neurocognitive disorder (American Psychiatric Association & American Psychiatric Association, 2013) and McKeith's criteria for the diagnosis of prodromal DLB (I. McKeith et al., 2020). Patients were defined as having mild DLB if they had an MMSE score between 20 and 25 and were diagnosed as having

probable DLB according to the current DLB criteria (I. G. McKeith et al., 2017). All participants benefited from a classic medical examination, which notably included evaluation of the features of parkinsonism using the Unified Parkinson's Disease Rating Scale (part 3): akinesia, rigidity and resting tremor (rated from 0 for no symptoms to 4 for serious symptoms). The DLB group underwent further clinical examination of DLB core criteria, among which fluctuations were assessed with the Mayo Clinic Fluctuations scale (Ferman et al., 2004) and the Newcastle-upon-Tyne Clinician Assessment of Fluctuation scale (Walker et al., 2000). The Parkinson's disease-associated psychotic symptoms questionnaire (Fénelon et al., 2010) was used to evaluate the presence of hallucinations. Rapid eye movement sleep behaviour disorder (RBD) was evaluated using a sleep questionnaire on RBD (Gjerstad et al., 2008), simplified into four questions, two each for the patient and for the caregiver: one concerning movements during sleep, the second concerning vivid dreams and nightmares.

Subjects with a history of alcohol/substance abuse, significant visual or auditory disabilities, relevant neurological of psychiatric comorbidities or the presence of other severe or unstable medical illnesses were not enrolled in the study. Subjects with an abnormal neurological examination – except for parkinsonism in the case of patients –, depression symptoms (mini-GDS, (Clément et al., 1997)) or a significant cerebral vascular burden (Modified Hachinski Ischemic Score > 7, (Hachinski et al., 1975)) were not enrolled. Participants with CSF biomarkers suggestive of Alzheimer's disease (i.e., abnormal Aβ42/Aβ40 ratio, t-Tau, phospho-Tau181) were not enrolled. Finally, participants with claustrophobia or contraindications to MRI were not enrolled. All participants provided written informed consent for the study, in accordance with the Declaration of Helsinki, and the study was approved by the ethics committee Sud Méditerranée III.

Behavioural Study

The HTT assesses the individual's accuracy through measuring the difference between perceived heartbeats and actual heartbeats (Garfinkel et al., 2015). The closer the count is to actual heartbeats, the greater is the accuracy. Participants were placed in a supine position with their arms at their sides. They were asked to close their eyes and try to feel the heartbeats in their chest, without measuring their pulse. When they were able to feel their heartbeats, they had to report it to the examiner, who then gave a go signal from which the participants had to start silently counting their heartbeats for 20 seconds. Simultaneously, the examiner measured the pulse on their left wrist. When the examiner gave the stop signal, participants were asked to report the number of heartbeats felt during the test. The task was repeated three times, alternating rest and perception periods like the following series: rest (20 sec) – perception (20 sec) – rest (20 sec) – perception (20 sec) – rest (20 sec) – perception (20 sec) – rest (20 sec).

Statistical analysis for the behavioural study

Student's *t* tests were used to compare intergroup differences between DLB patients and control subjects for demographic quantitative data. A chi-squared test was used to compare the sex ratio between groups. For the HTT, as proposed by Schandry (Schandry, 1981), we used an "interoceptive accuracy score", equal to 1 minus the difference between reported and actual number of heartbeats, divided by the actual number of heartbeats (see equation 1). The error score was obtained as the average of the absolute values of the three quotients

Equation 1

$$\text{Interoceptive accuracy} = 1 - \left| \frac{\textit{actual heartbeat} - \textit{counted heartbeat}}{\textit{actual heartbeat}} \right|$$

(from the three perception phases). Thus, a low average error score reflected a poor accuracy of perception during all the three trials. Namely, when participants did not detect their heartbeats during a trial, they obtained a reported heartbeat score of zero, an error score of 1 and an interoceptive accuracy score of 0.

To control possible training effects from trial 1 to trial 3, ANOVA using the Greenhouse Geisser correction was used. Mann-Whitney *U* tests were then used to compare the average error score between DLB patients and the controls. Moreover, as some DLB patients displayed severe interoceptive deficit, we divided the DLB group in two subgroups, and used Student's *t* test to compare clinical symptoms such as fluctuations, hallucinations, RBD and MMSE score, between patients with severe interoceptive disorders and patients with mild or no interoceptive disorders.

Neuroimaging Study

Each participant underwent a high-resolution anatomical MRI scan within a maximum of 12 weeks after taking the AI. T1-weighted three-dimensional anatomical images were obtained using a 3T MRI scanner (Verio 32-channel Tim Siemens scanner; Siemens, Erlangen, Germany) using a volumetric magnetization-prepared rapid acquisition with gradient-echo (MPRAGE) sequence (FOV = 256 × 256 mm^2, image matrix = 256 × 256, slice thickness = 1 mm, repetition time = 1900 ms, echo time = 2.52 ms, flip angle = 9°).

Voxel-Based Morphometry Analyzes

We used voxel-based morphometry (VBM) to investigate differences in cortical thickness between the healthy controls and the DLB patients and to examine the neuroanatomical substrates of prereflective SSS, measured by interoceptive accuracy, in DLB patients. We first wanted to use voxel-based morphometry (VBM) to test the correlations between grey matter

volume and interoceptive accuracy, but we were unable to do so, because behavioural results were not normally distributed in our populations. We therefore opted for a comparative analyzes to investigate differences in grey matter volume of the insular cortex, between DLB patients with severe interoceptive disorders (n = 12) and DLB patients with mild or no interoceptive disorders (n = 8). However, in the absence of significant differences at P <.005, between the two groups of patients, we finally chose to compare each patients' group (i.e. DLB patients with severe interoceptive disorders (n = 12), on the one hand, and DLB patients with mild or no interoceptive disorders (n = 8) on the other hand), versus the control group (n = 20), using a threshold corrected with Family-Wise Error (FWE) between P = 0.05 and P = 0.0005, as we sought the significant threshold corrected with FWE at which it would exist possible diminished grey matter volume in the insula, only in the group of DLB patients with severe interoceptive disorders. VBM analyses included image preprocessing and statistical analyses. These steps were carried out using the SPM12 software package (Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/) running on Matlab R2017b (MathWorks, Natick, MA, USA). Anatomical MRI images were spatially preprocessed using standard procedures (Good et al., 2001). All T1-weighted structural images were first segmented, bias-corrected and spatially normalized to the Montreal Neurological Institute space using an extension of the unified segmentation procedure that includes six classes of tissue (Ashburner & Friston, 2005). The DARTEL registration toolbox was then used to build a study-specific template and to bring into alignment all of the segmentation images. The VBM analysis was done on modulated grey matter (GM) images; that is, the GM value in each voxel was multiplied by the Jacobian determinant derived from the spatial normalization. This procedure preserves the total amount of GM from the original images. These modulated GM images were smoothed with a Gaussian kernel (full width at half maximum [FWHM]:

8 mm). Between-group voxel-based comparisons were displayed after correcting for multiple comparisons with false discovery rate (FDR; $P < .05$).

Results

Clinical characteristics

A description of the study population is presented in Table 1. Groups were well matched for age (t = .64, P = .526), years of education (t = *-1*.61, P = .116) and sex (χ^2 = .44, P = .507). The DLB group comprised 13 patients at the prodromal stage of DLB and 7 patients at the mild stage of the disease. Among the 20 DLB patients, 85% presented fluctuations, 60% presented hallucinations or illusions, and 60% presented RBD. Concerning parkinsonism features, akinesia was observed in 80% of DLB patients, rigidity in 70% of DLB patients and resting tremor in only one patient (5%).

Table 1 Demographic and clinical characteristics of the DLB group and the control group

Characteristic	**DLB group (*n* = 20)**	**Control group (*n* = 20)**	**Student's *t* test or chi-squared test**
Mean age in years (+SD)	71.9 (7.9)	70.6 (7.4)	t = .53, P = .598
Years of education (+SD)	12.7 (2.5)	14.2 (2.8)	t = *-1*.70, P = .096
Sex, M/F	14/6	12/8	χ^2 = .44, P = .507
MMSE score (/30)	26.3 (2.39)	28.8 (1.0)	*t = -4.32*, *P* < .001
Handedness, R/L	19/1	20/0	χ^2 = 1.03, P = .311
Fluctuations (%)	17/20 (85)	N/A	
Hallucinations/illusions (%)	12/20 (60)	N/A	
RBD (%)	12/20 (60)	N/A	
Parkinsonism			
Akinesia (%)	16/20 (80)	N/A	
Rigidity (%)	14/20 (70)	N/A	
Tremor at rest (%)	1/20 (5)	N/A	

DLB, dementia with Lewy bodies; SD, standard deviation; M, male; F, female; MMSE, Mini-Mental State Examination; R, right; L, left; RBD, rapid eye movement sleep behaviour disorder; N/A, not applicable.

Significant P and χ^2 values are in italics.

Behavioural study

For the HTT, Mann-Whitney *U* tests showed significant inferior interoceptive accuracy average error scores in the DLB group (0.30, SD 0.39) in comparison to the controls (0.82, SD 0.24), (*U* = 57, *P* <.0001). Figure 1 shows the frequency distribution of the average error scores during the three trials, for DLB patients (A) and controls (B). In DLB patients, 60% of the subjects did not perceive their heartbeat at all, for each of the three trials, whereas 90% of the controls ranged between the values 0.6 and 1.

The raw data were checked for training effects: no improvement from trial 1 to trial 3 was observable, as confirmed by an ANOVA using the Greenhouse Geisser correction (F (1.24, 72.9) = 1.85, *P* = 0.18).

For the comparison of clinical symptoms between DLB patients with severe interoceptive disorders and DLB patients with mild or no interoceptive disorders, Student's *t* tests did not find any significant differences either in fluctuations (*t* = -0.99, *P* = 0.33), nor hallucinations (*t* = -0.72, *P* = 0.48), nor RBD (*t* = -0.72, *P* = 0.48), nor MMSE (*t* = 0.49, *P* = 0.63).

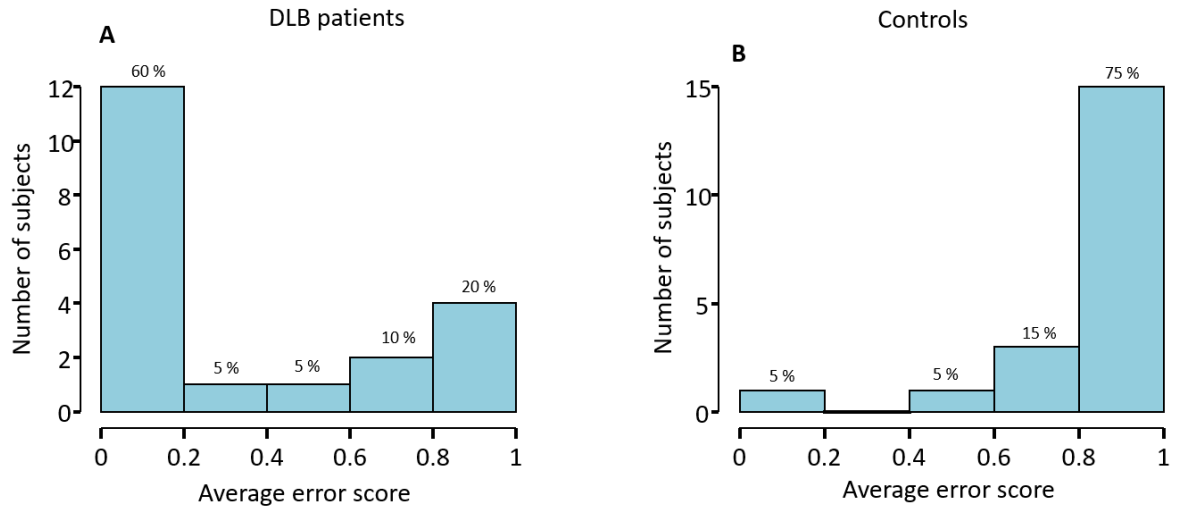

Figure 1 Distribution of average error scores during the three trials, among Dementia with Lewy bodies patients (A) and controls (B)

Neuroimaging study

A voxel-based analysis comparing cortical thickness in DLB patients versus healthy controls is presented in the Supplementary Material. The analysis included TIV and age as nuisance covariates and revealed patterns of cerebral atrophy, with diminished grey matter volume in the insular, temporal, occipital, frontal and cingular cortices, and to a lesser extent the parietal cortex, and also in the cerebellum and subcortical regions such as the putamen ($P < .05$, FDR corrected), when compared to healthy controls. VBM analyzes comparing DLB patients with severe interoceptive disorders and DLB patients with mild or no interceptive disorders were corrected with Family-Wise Error (FWE) at $P = 0.005$, and showed a greater reduction of grey matter volume in bilateral insulae, right ACC, right putamen, right parahippocampus and left superior temporal gyrus, in DLB patients with severe interoceptive disorders compared to DLB patients with mild or no interoceptive disorders (see figure 2). Specifically, in DLB patients with severe interoceptive disorders, the cluster size in the insulae was $k = 115$ in right insula and $k = 36$ in left insula, compared to $k = 38$ in right insula and $k = 17$ in left insula, in DLB patients with mild or no interoceptive disorders. When the stat was increased at $P = 0.0005$ (FWE corrected), results remained significant only in DLB patients with severe interoceptive disorders, with reduction of grey matter volume in bilateral insulae, right ACC, right putamen, and in right parahippocampus.

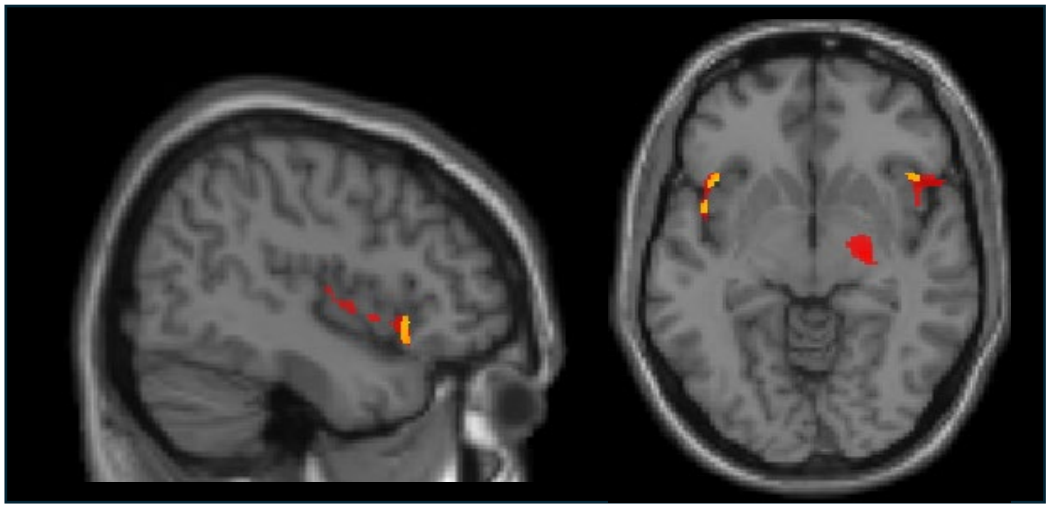

Figure 2. VBM comparative analyzes in Dementia with Lewy bodies patients with severe interoceptive disorders and DLB patients with mild or no interoceptive disorders, compared to controls.

Greater reduction of grey matter volume in bilateral insulae, right ACC, right putamen, right parahippocampus and left superior temporal gyrus in DLB patients displaying severe interoceptive disorders (red) than DLB patients displaying mild or no interoceptive disorders (yellow), using a threshold corrected with FWE, at $P = 0.005$, including age, total intracranial volume and MMSE as nuisance covariates, $k = 50$.

Discussion

This study is the first to investigate the SSS, and more particularly bodily awareness in DLB patients, through the study of interoceptive abilities. In accordance with our hypothesis, we found that DLB patients showed profound impairments of interoceptive accuracy, with more than half of the patients not detecting their heartbeats, whereas almost all the control subjects presented high interoceptive accuracy scores. Moreover, as we hypothesized, DLB patients with severe interoceptive disorders displayed greater atrophy of bilateral insulae than DLB patients with mild or no interoceptive disorders, compared to control subjects.

Accumulating evidence in the literature suggests that DLB is marked by modifications of very elaborated components of the self, such as the self-concept (Philippi et al., 2020; Tisserand et al., 2020, 2023) and autobiographical memory (Tisserand et al., 2024) which would both rely on the SSS (Prebble et al., 2013). The present study is the first to demonstrate, through a severe interoceptive deficit, that the SSS is impaired in DLB, as is the case in other dementia such as bvFTD (Hazelton et al., 2023) We also found that DLB patients with severe interoceptive disorders presented greater atrophy in bilateral insulae, right ACC, putamen, parahippocampus, and in left superior temporal gyrus, compared to DLB patients with mild or no interoceptive disorders. The insular cortex and ACC are key nodes underpinning interoception (Craig, 2002; Critchley et al., 2004; Critchley & Harrison, 2013). A few studies in dementia have already shown that there is a relationship between interoceptive impairments and atrophy in the insula and the ACC (Garcia-Cordero et al., 2016; Salamone et al., 2021). Furthermore, a recent study exploring interoception in dementia (Hazelton et al., 2023) found that bvFTD patients displayed impaired interoceptive accuracy on a heartbeat detection task that was correlated with insular reduced integrity, whereas no cluster were identified in AD

or PD patients, neither interoceptive deficits. Moreover, authors found that, in bvFTD patients, interoceptive deficit contributed to significant impairment in the ability to recognise emotions, which was also associated to atrophy in insular cortices. This is in line with the hypothesis according to which insular cortex is specifically involved in functions with different levels of awareness (Craig, 2009; Damasio, 1993; Silani et al., 2008).

The SSS is considered to imply a very low level of consciousness, classified as ”prereflective”, involving an immediate and ongoing perceptual stream of experience (Christoff et al., 2011; Gallagher, 2000; Prebble et al., 2013; Vandekerckhove & Panksepp, 2009) and a higher level of consciousness, classified as “self-awareness”, involving a reflective and metaconscious experience which develops out of prereflective consciousness. On the one hand, this prereflective self experience is necessary to encode the egocentric subjective perspective, that will provide the basis of episodic memories (Levine et al., 2002; Moscovitch, 1995). On the other hand, episodic memory in turn would rely on a self-aware conscious state called “autonoetic consciousness” (Feinberg & Keenan, 2005; Tulving, 2002, 2005; Vandekerckhove & Panksepp, 2009) which consists of a subjective awareness of the self extended in time, but which also presuppose self-awareness in the present moment (Keenan et al., 2000; Stuss et al., 2001; Wheeler et al., 1997). This perspective suggests that SSS is necessary for episodic – autobiographical – memory both at the time of encoding and at the time of retrieval. Regarding the detection of heartbeat more specifically, it likely contributes to the genuine feeling of re-experiencing the emotional aspects associated with specific autobiographical memories, and ultimately helps integrate the memory as belonging to the self. The SSS is also the conscious and reflective part of the self that constructs the mental representations of self, or “self-concept” (Lewis, 1991; Martin, 2005, p. 200; Morin & Everett, 1990; Singer, 1995), which is made up of autobiographical knowledge and refers to the way we internally represent

who we are. These two elaborated components of the self (i.e. autobiographical memory and self-concept) which are both grounded on the SSS are impaired and related to insular damage in DLB (Philippi et al., 2020; Tisserand et al., 2020, 2023, 2024). The present study demonstrated that the elementary aspects of the SSS is impaired in DLB, and that the severity of its impairment is related to insular atrophy. These findings support the hypothesis that insular atrophy can result in SSS impairments, that leads to the global collapse of the self.

Overall, our study has some limitations. In particular, the sample sizes were relatively small (n = 20 in each group) and the behavioural scores were not normally distributed, compelling us to do VBM comparative analyzes, instead of testing the correlations with behavioural scores and grey matter volume. Moreover, considering that DLB is marked by lesions of the sympathetic nerve of myocardium (Hanyu et al., 2006; I. G. McKeith et al., 2017), we cannot exclude that a failure of the interoceptive signal could be partially due to peripheral denervation, and not only from insular damage. Consequently, future studies involving a larger cohort of DLB patients will be needed to confirm our findings. Therefore, our future work aims to investigate the relationship between the SSS, the self-concept and autobiographical memory in DLB, with a special focus on insula's role within the self.

Conclusion

To our knowledge, this is the first study to assess interoception in DLB with a heartbeat detection task, from behavioural and neuroimaging angles. We found that DLB patients display profound interoceptive disorders, suggesting impairments of the prereflective SSS, which is the most elementary component of the SSS. This in in line with previous evidence showing impairments of more elaborated self components, such as the self-concept and autobiographical memory, that would both rely on the SSS. We also found that more

pronounced interoceptive deficit was related to greater insular atrophy, as is the case for the self-concept and autobiographical memory deficits. Through the present work, we suggest that early insular atrophy in DLB would give rise to impairments of the SSS, thus leading to a global collapse of the self, impacting more elaborated components such as the self-concept and autobiographical memory.

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Competing interest

None of the authors have any competing financial of non-financial interests to declare in relation to the current work.

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CONCLUSION ÉTUDE 1 : À travers cette première étude, nous avons montré, pour la première fois, qu'il existe dans la MCL un déficit sévère des capacités intéroceptives, qui s'inscrivent dans le sens subjectif de soi préréflexif. En effet, plus de 60% des patients de notre échantillon ne percevaient pas leurs battements cardiaques, alors qu'à l'inverse, 90% des sujets témoins présentaient une haute sensibilité intéroceptive. De plus, nous avons observé que les patients qui montraient des capacités intéroceptives altérées présentaient une atrophie insulaire plus marquée que les patients chez qui les capacités intéroceptives étaient relativement préservées.

Les résultats de cette étude suggèrent l'existence d'un déficit profond du sens subjectif de soi en lien avec l'atrophie insulaire dans la MCL, et plus particulièrement de l'expérience préréflexive, dont l'existence est supposée être la condition *sine qua non* à l'émergence des autres composantes (Prebble et al., 2013). C'est à travers l'expérience préréflexive qu'émerge le sentiment que notre personne est le sujet de l'expérience vécue, qu'il s'agisse d'un phénomène interne comme les battements du cœur, ou d'un phénomène externe comme la sensation de l'air frais que l'on respire. L'expérience préréflexive constitue, par ailleurs, le prérequis d'un niveau de conscience quelque peu plus élaboré, auquel Prebble et collaborateur se réfère par le terme de « *self-awareness* », qui implique une conscience réflexive, permettant l'analyse de ses pensées, sentiments, comportements, expériences (Keenan et al., 2005; Leary & Tangney, 2012; Lewis, 1991; Schooler, 2002; Stuss & Levine, 2002). Si le sens subjectif de soi dans sa forme préréflexive est nécessaire à l'encodage de l'expérience subjective, qui servira de base à la mémoire autobiographique (Levine et al., 2002; Moscovitch, 1995), il permettrait également, grâce à sa dimension réflexive, de voyager mentalement dans le temps par le biais de la conscience autonoétique, afin de rappeler les souvenirs autobiographiques (Feinberg & Keenan, 2005; Tulving, 2002, 2005; Vandekerckhove, 2009). Dans le cas particulier de la perception des battements cardiaque, cette faculté pourrait participer à l'émergence de la sensation de reviviscence de la composante émotionnelle caractéristique des souvenirs autobiographiques épisodiques, ainsi que le sentiment d'appartenance à soi. De plus, le sens subjectif de soi permettrait la construction des représentations mentales du self, à savoir le self-conceptuel (Lewis, 1991; Martin, 2005; Morin & Everett, 1990; Singer, 1995), qui est, en partie constitué des connaissances que l'on a sur soi, et qui renvoie à la façon dont on se représente

intérieurement. Du point de vue anatomique, le sens subjectif de soi reposerait en parti sur l'insula, conformément à ce qui a déjà été proposé dans plusieurs études (Craig, 2003; Devue et al., 2007; Farrer et al., 2003; Farrer & Frith, 2002; Tsakiris, 2008). L'insula pourrait ainsi être impliquée dans un schéma plus complexe de conscience de soi, conférant le sentiment de soi, et permettant de discriminer ce qui appartient au soi, de ce qui appartient au non-soi. Finalement, c'est le sens subjectif de soi, à la base de l'organisation hiérarchique du self, qui permettrait de reconnaitre un souvenir ou un attribut comme lui appartenant. Dans la mesure où le sens subjectif de soi serait étroitement lié, et servirait de fondation aux composantes plus sophistiquées du self, nous postulons que son altération secondaire à l'atteinte de la région insulaire, sur laquelle il repose en partie, pourrait mener à un effondrement global du self, impactant les composantes qui en découlent tels que le self-conceptuel et la mémoire autobiographique.

3. Étude du self conceptuel dans la MCL

Qui suis-je avec mes corps de Lewy ? L'insula, une région centrale du self-conceptuel

À travers cette deuxième étude, nous souhaitions évaluer le self-conceptuel et ses substrats neuroanatomiques, avec un intérêt particulier pour l'insula. Le self-conceptuel fait référence aux connaissances sur soi-même, telles que les traits de personnalités, valeurs, statuts sociaux, caractéristiques physiques ou encore les goûts personnels. Le self-conceptuel est alimenté par un « corpus de connaissances autobiographiques » et renvoi à la façon dont on se représente. S'il est admis que le self-conceptuel repose principalement sur les régions de la ligne corticale médiane (Kjaer et al., 2002), il a également été souligné que l'insula semblait jouer un rôle particulier dans les processus de référence à soi (Modinos et al., 2009).

Après avoir montré qu'il existait un déficit du sens subjectif de soi dans la MCL, nous souhaitions analyser, à travers cette étude comportementale et de neuroimagerie, l'impact de l'atteinte insulaire sur le self-conceptuel dans la MCL. Nous avons utilisé le TST comme mesure du self-conceptuel, qui est un questionnaire dans lequel les participants devaient répondre à la question « qui suis-je », en donnant le plus d'affirmations les caractérisant. Les scores comportementaux étaient ensuite comparés entre les patients atteints de MCL et les sujets témoins, et corrélés à la volumétrie cérébrale.

Dans la mesure où le sens subjectif de soi est déficitaire dans la MCL, et en supposant que l'insula tient un rôle central dans les réseaux cérébraux du self, nous avons fait l'hypothèse qu'il existait des altérations du self-conceptuel dans la MCL, et qu'elles seraient corrélées à l'atrophie insulaire, parmi d'autres régions impliquées dans le self-conceptuel.

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Who am I with my Lewy bodies? The insula as a core region of the self-concept networks

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Abstract

Background Dementia with Lewy bodies (DLB) is characterized by insular atrophy, which occurs at the early stage of the disease. Damage to the insula has been associated with disorders reflecting impairments of the most fundamental components of the self, such as anosognosia, which is a frequently reported symptom in patients with Lewy bodies (LB). The purpose of this study was to investigate modifications of the self-concept (SC), another component of the self, and to identify neuroanatomical correlates, in prodromal to mild DLB.

Methods Twenty patients with prodromal to mild DLB were selected to participate in this exploratory study along with 20 healthy control subjects matched in terms of age, gender, and level of education. The Twenty Statements Test (TST) was used to assess the SC. Behavioral performances were compared between LB patients and control subjects. Three-dimensional magnetic resonance images (MRI) were acquired for all participants and correlational analyses were performed using voxel-based morphometry (VBM) in whole brain and using a mask for the insula.

Results The behavioral results on the TST showed significantly impaired performances in LB patients in comparison with control subjects ($p < .0001$). Correlational analyses using VBM revealed positive correlations between the TST and grey matter volume within insular cortex, right supplementary motor area, bilateral inferior temporal gyri, right inferior frontal gyrus, and left lingual gyrus, using a threshold of $p = .001$ uncorrected, including total intracranial volume (TIV), age, and MMSE as nuisance covariates. Additionally, correlational analysis using a mask for the insula revealed positive correlation with grey matter volume within bilateral insular cortex, using a threshold of $p = .005$.

Conclusions The behavioral results confirm the existence of SC impairments in LB patients from the prodromal stage of the disease, compared to matched healthy controls. As we expected, VBM analyses revealed involvement of the insula, among that of other brain regions, already known to be involved in other self-components. While this study is exploratory, our findings provide important insights regarding the involvement of the insula within the self, confirming the insula as a core region of the self-networks, including for high-order self-representations such as the SC.

Keywords *Self*, *Self-concept*, *Insula*, *Dementia with lewy bodies*, *Lewy bodies*, *Semantic knowledge*

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Introduction

Dementia with Lewy bodies (DLB) is the second most common form of cognitive neurodegenerative disease after Alzheimer's disease (AD), with prevalence rates of up to 5% in the elderly population and up to around 20% of all cases of dementia [1, 2]. While visual hallucinations are frequently present in patients with Lewy bodies (LB), other behavioral disturbances such as anosognosia also frequently occur (Calil et al., 2021) and could be related to an alteration of the self-consciousness. DLB is characterized by insular atrophy, occurring from the early stage of the disease [3–6], the insula being a core region for the self [7].

The insula is indeed involved in a wide variety of processes related to the self, from the most internal bodily states, such as interoception [8, 9] to high-order processes such as knowledge about oneself [10], that belong to the self-concept (SC). The SC encompasses different types of self-knowledge, such as attributes, traits, beliefs, values, social status, roles, physical characteristics or even personal preferences [11, 12]. It is made up of a body of autobiographical knowledge and refers to the way we internally represent who we are, determining what sort of person we are. The SC is closely linked to autobiographical memory, and particularly to its semanticized form, which contributes to the formation and maintenance of mental representation of the self in the present moment and across time [13–20]. Thus, behavioral and neuroimaging studies are increasingly addressing tasks related to the SC, through methods exploring personal identity. In a study investigating reflective self-referential processes, healthy subjects were asked to think intensely on how they would describe their own personality traits and physical appearance. Self-referential conditions (personality traits and physical appearance) induced activation in various cortical midline structures (CMS), including the medial prefrontal cortex (MPFC), the anterior cingulate cortex, the supplementary motor area (SMA), and the precuneus, when compared to non-self-referential conditions (i.e., thoughts about a famous person, the Danish Queen) [21]. Another study explored brain activity whilst subjects were reflecting upon their own personal qualities as compared to those of an acquaintance. For both conditions, researchers found activations in the ACC, MPFC, SMA, and superior temporal gyrus, with significantly greater activations in the self condition. Interestingly, the insula showed unique activity associated with self-reflection, highlighting a key role for the insula in self-referential processes [10].

Hence, the aim of the present study was to better understand the impact of neurodegeneration on the SC in patients with prodromal to mild DLB, and to explore the underlying structural mechanisms, with a particular focus on the link between SC and the insula. Regarding this relationship, our team has previously highlighted the existence of modifications of the SC in LB patients from the prodromal stage, in an experiment on personal tastes. By means of a questionnaire, we demonstrated that LB patients presented significant changes in tastes in both food and non-food domains, independently of the existence of anosmia or agueusia. Moreover, we found that these changes were associated with grey matter atrophy in the insula [22], suggesting a role for the insula in supporting personal tastes as self-concepts. Based on the fact that the insula is a key region for the self and given that this region is atrophied at an early stage in LB patients, we posit that impairments of the SC would be observed in LB patients, and would be correlated to insular atrophy, among other regions involved in self-concept.

Methods

Study population

Twenty prodromal to mild DLB patients and 20 healthy control subjects matched for age, gender and level of education (with a minimum of 9 years) were enrolled in the present study between January 2021 and February 2023. A description of the study population is presented in Table 1. Patients were recruited from the tertiary memory clinic of Strasbourg University Hospital, France, including the Geriatrics and Neurology Departments. Control subjects were recruited among friends and relatives of the patients, via the listing of controls of the local clinical investigation center and from the control group of the AlphaLewyMA cohort (http://clinicaltrials.gov/ct2/show/NCT01876459).

The LB group comprised 14 men and 6 women aged from 60 to 80 years (mean=71.95, standard deviation [SD]=7.99). Diagnosis of prodromal and mild DLB patients was based on core clinical features [23, 24]. Some of the patients had also benefited from biomarkers during their clinical follow-up. Indeed a dopamine transporter SPECT (DAT) scan was realized when parkinsonism was doubtful, and cerebrospinal fluid (CSF) analysis was realized when an amnestic syndrome of hippocampal type suggested a possible Alzheimer's disease, to ensure that there was no co-pathology. Patients with prodromal DLB were defined as having mild cognitive impairment if they had a Mini-Mental State Examination (MMSE) [25] score≥26, had preservation of independence as assessed by the Instrumental Activities of Daily Living [26], and fulfilled both the DSM-5 criteria of mild neurocognitive disorder [27] and McKeith's criteria for the diagnosis of prodromal DLB [23]. Patients were defined as having mild DLB if they had an MMSE score between 20 and 25 and were diagnosed as having probable DLB according to the current DLB criteria [24]. Thus, 13 of the 20 patients were in the prodromal stage of DLB and the remaining seven were in the mild stage of the disease. Dopamine

transporter SPECT (DAT) scan was available to support the diagnosis in approximately a quarter of the patients. CSF analysis was available to confirm that there was not associated Alzheimer's disease in approximately half of the patients. All participants benefited from a classic medical examination, which notably included evaluation of the features of parkinsonism using the Unified Parkinson's Disease Rating Scale (part 3): akinesia, rigidity, and tremor at rest (rated from 0 for no symptoms to 4 for serious symptoms). The LB group underwent further clinical examination of DLB core criteria, among which fluctuations were assessed with the Mayo Clinic Fluctuations scale [28] and the Newcastle upon Tyne Clinician Assessment of Fluctuation scale [29]. The Parkinson's disease-associated psychotic symptoms questionnaire [30] was used to evaluate the presence of hallucinations. Rapid eye movement sleep behavior disorder (RBD) was evaluated using a sleep questionnaire on RBD [31], simplified into four questions each for the patient and the caregiver: one concerning movements during sleep, the second concerning vivid dreams and nightmares. Among the 20 LB patients, 85% presented fluctuations, 60% presented hallucinations or illusions, and 60% presented RBD. Concerning parkinsonism features, akinesia was observed in 80% of LB patients, rigidity in 70% of LB patients, and tremor at rest in only one patient (5%) (see Table 1).

Participants with history of alcohol/substance abuse, significant visual or auditory disabilities, relevant neurological of psychiatric comorbidities, or the presence of other severe or unstable medical illnesses were not enrolled in the study. Participants with an abnormal neurological examination – except for parkinsonism in the case of patients –, depression symptoms (mini-GDS [32]), , or a significant cerebral vascular burden (Modified Hachinski Ischemic Score scale>7 [33]), were not enrolled. Participants with CSF biomarkers in favor of an Alzheimer's disease (i.e. abnormal Aβ42/Aβ40 ratio, t-Tau, phospho-Tau181) were not enrolled. Finally, participants with claustrophobia or contraindications to MRI were not enrolled. All participants provided written informed consent for the study, in accordance with the Declaration of Helsinki, and the study was approved by the local Ethics committee (Sud Méditerranée III).

Table 1 Demographic and clinical characteristics of the LB group and the control group

Characteristic	LB group ($n=20$)	Control group ($n=20$)	Student's t test or chi-squared test
Age (years)	71.9 (7.9)	71.2 (7.6)	$t=0.28$, $p=.778$
Years of education	12.2 (2.2)	14.8 (4.1)	$t=-2.54$, $p<.05$
Sex, M/F	14/6	12/8	$\chi2=0.44$, $p=.507$
MMSE score (/30)	26.3 (2.39)	28.8 (1.0)	$t=-4.32$, $p<.001$
Handedness, R/L	19/1	20/0	$\chi2=1.03$, $p=.311$
Fluctuations (%)	17/20 (85)	N/A	
Hallucinations/illusions	12/20 (60)	N/A	
RBD	12/20 (60)	N/A	
Parkinsonism			
Akinesia (%)	16/20 (80)	N/A	
Rigidity (%)	14/20 (70)	N/A	
Tremor at rest (%)	1/20 (5)	N/A	

LB Lewy bodies, *M* male, *F* female, *MMSE* Mini-Mental State Examination, *R* right, *L* left, *RBD* rapid eye movement sleep behavior disorder, *N/A* not applicable

Standard deviations for age and years of education are shown in parentheses. Significant p and χ2 values are in italics

Behavioral study

All participants underwent an evaluation of the SC. We also assessed general cognitive functioning and verbal fluency in LB patients.

General cognitive functioning

General cognitive functioning was assessed with the MMSE, and the maximum score was 30 points.

Verbal fluency

Verbal fluency was assessed with a task in which patients had two min to generate as many words as they could beginning with the letter P. Proper nouns and variations on words (e.g., "photograph" and "photography") were not allowed. The score was the number of correctly generated words.

Twenty statements test

The assessment of the SC was performed with the Twenty Statements Test (TST; [34]). The TST requires the subjects to make up to 20 statements in response to the question "Who am I?". They were asked to write down each of the statements by completing the sentence "I am…". To avoid any potential limitations due to impairment in generative strategies, cues indicating different possible categories of responses among five domains of identity (i.e., personal, family, social, moral, and physical) were given to the two groups of participants, as well as examples for each possible category of response. Instructions and cues were written down on the response sheet and an oral administration of the test was used for DLB patients in order to facilitate responses. For the purposes of this study, we only considered the number of responses provided by the participant, regardless of the category. Repeated responses and responses that did not answer the question of interest were not considered.

Statistical analyses for the behavioural study

Student's *t* test was used to compare intergroup differences between LB patients and control subjects for both

demographic and behavioral quantitative data. For the behavioral data, a one-tailed t test was used, since we hypothesized that LB patients would have lower scores than control subjects due to impairment of the SC. We also analyzed correlations using Pearson's test, between the TST and MMSE scores, and between the TST and verbal fluency scores.

A chi-squared test was used to compare the sex ratio between groups. A threshold of $p<.05$ was used to determine statistical significance.

Neuroimaging study

Each participant underwent a high-resolution anatomical MRI scan within a maximum of 12 weeks after taking the TST. T1-weighted three-dimensional anatomical images were obtained using a 3T MRI scanner (Verio 32-channel Tim Siemens scanner; Siemens, Erlangen, Germany) using a volumetric magnetization-prepared rapid acquisition with gradient-echo (MPRAGE) sequence (FOV=256×256 mm, image matrix=256×256, slice thickness=1 mm, repetition time=1900 ms, echo time=2.52 ms, flip angle=9°).

Voxel-based morphometry analyses

We used voxel-based morphometry (VBM) to investigate differences in grey matter volume between the healthy controls and the LB patients, and to examine the neuroanatomical correlates of the SC in both the healthy controls and LB patients. VBM analyses included image preprocessing and statistical analyses. These steps were carried out using the SPM12 software package (Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/) running on Matlab R2017b (MathWorks, Natick, MA, USA). Anatomical MRI images were spatially preprocessed using standard procedures [35]. All T1-weighted structural images were first segmented, bias-corrected, and spatially normalized to the Montreal Neurological Institute space using an extension of the unified segmentation procedure that includes six classes of tissue [36]. The DARTEL registration toolbox was then used to build a study-specific template and to bring into alignment all of the segmentation images. The VBM analysis was done on modulated grey matter (GM) images; that is, the GM value in each voxel was multiplied by the Jacobian determinant derived from the spatial normalization. This procedure preserves the total amount of GM from the original images. These modulated GM images were smoothed with a Gaussian kernel (full width at half maximum [FWHM]: 8 mm). Between-group voxel-based comparisons were displayed after correcting for multiple comparisons with false discovery rate (FDR; $p<.05$). To map the regions of atrophy related to disorders of the SC, we tested the correlation between the GM volume at a voxel level and the total score on the TST using the general linear model. Correlation analysis between behavioral data and GM volume was performed using a threshold of $p=.001$ uncorrected, including total intracranial volume (TIV) and age as nuisance covariates. MMSE was also considered as an additional covariate to investigate the potential impact of disease severity. A cluster spatial extent of 50 voxels was used to avoid irrelevant and isolated detections. The software Xjview (http://www.alivelearn.net/xjview8/) allowed us to characterize each cluster.

Moreover, to ensure that finding the insula was not a spurious result, when considering the number of covariates and that we did not use correction for multiple comparison, we completed the VBM analyses in whole brain, with a VBM analysis using a mask for the insula. The GM images were smoothed at 4 mm to increase specificity in order to discriminate true effect from random noise. We used a threshold of $p<.005$, including the same covariates as for the whole brain analyses.

Results

Behavioral study

The behavioral results indicated that the LB group had significantly decreased performances for the total score on the TST compared to the healthy controls (mean 9.7, SD 4.5 vs. 19.05, SD 3.36, $t=7.38$, $p<.0001$). We completed correlational analyses in the LB group by examining correlations between the TST and MMSE scores, which revealed significant correlations ($r=.49$, $p<.05$). We also analyzed correlations between the TST and verbal fluency scores, which showed significant correlations ($r=.55$, $p<.05$).

Neuroimaging study

Voxel-based analysis comparing grey matter volume in LB patients versus healthy controls is presented in supplementary material. Analysis included TIV and age as nuisance covariates, and revealed patterns of cerebral atrophy typically reported in LB patients [4], with grey matter volume in insular, temporal, occipital, frontal, cingular cortices and to a lesser extent parietal cortex ($p<.05$, FDR corrected), in LB patients compared to healthy controls.

In the LB group, correlational analysis for the SC revealed positive correlations with GM volume within right insular cortex (see Fig. 1), right SMA (see Fig. 2), right inferior frontal gyrus, left lingual gyrus and bilateral inferior temporal gyri (see Fig. 3), using a threshold of $p=.001$ uncorrected, including TIV, age, and MMSE as nuisance covariates, with a minimum cluster size of $k=50$ (Table 2). Correlational analysis for the SC, using a mask for the insula revealed positive correlation with GM volume within bilateral insular cortex (see Fig. 4), using a threshold of $p=.005$ uncorrected, including TIV, age, and

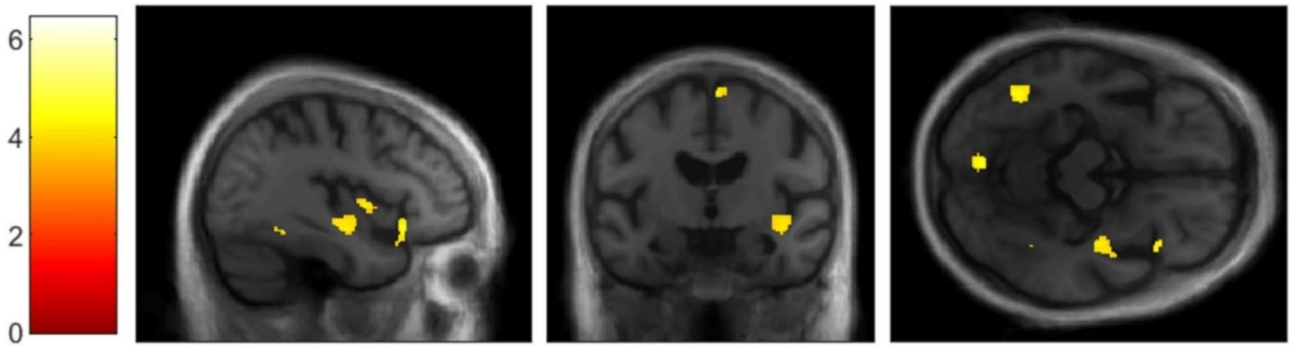

Fig. 1 VBM analyses for self-concept in the Lewy bodies group.Grey matter volumes within right insular cortex positively correlated with the total score on the TST questionnaire (self-concept), using a threshold of $p = .001$ uncorrected, including age, TIV and MMSE score as nuisance covariates, $k = 50$

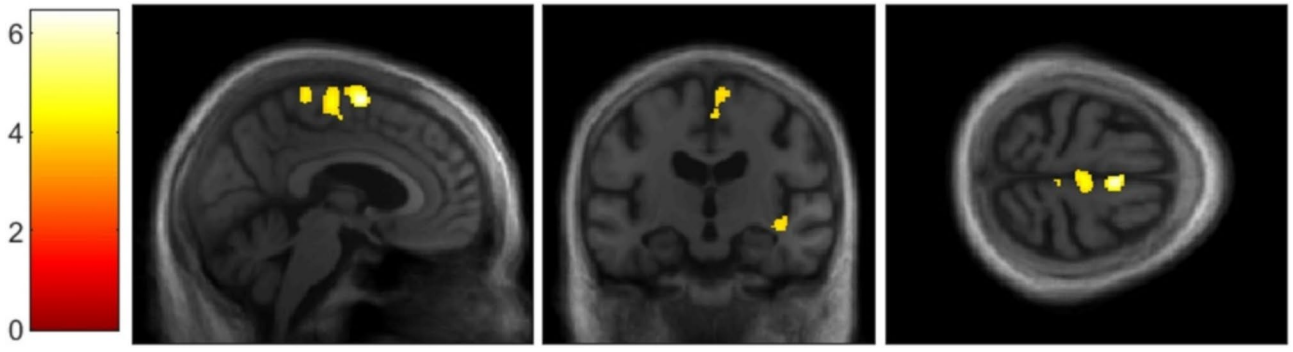

Fig. 2 VBM analyses for self-concept in the Lewy bodies group.Grey matter volumes within right supplementary motor area positively correlated with the total score on the TST questionnaire, using a threshold of $p = .001$ uncorrected, including age, TIV, and MMSE score as nuisance covariates, $k = 50$

MMSE as nuisance covariates. The correlational analyses did not reveal any correlation in the healthy controls.

Discussion

This study is the first to examine SC in LB patients by using a standardized measure. In summary, the findings indicate the existence of significant impairments of the SC in LB patients from the early stage of the disease, compared to age-matched healthy controls. Concordant with our hypothesis, imaging analyses confirmed the involvement of insular cortex atrophy in SC impairments, among other brain regions such as the SMA. These results bring new insight into the role of the insular cortex in the conception of oneself, among other brain regions more widely associated with classic self-networks.

We focused in particular on the role of the insula in the SC, with the hypothesis that insular atrophy could explain alterations of the self in LB patients. The insular cortex is commonly associated with interoceptive awareness [37] and socio-emotional processes [9]. It has also been associated with self-reflection upon personal qualities [10] and with self-esteem, two abilities that are related to the SC [38]. Regarding LB patients, our study is the first to highlight a diminished SC in relation to the insular atrophy that occurs early in the course of the disease [3–6]. SC impairments have already been linked to the atrophy of this structure in DLB, regarding modifications of personal tastes [22]. However, from the perspective of cognitive models of the self, personal preferences also imply the subjective sense of self, since liking or disliking an object is inherent to the subject in the present moment. In our study, to measure the SC in isolation from the subjective sense of self, we asked the participants to simply answer the question "who am I?", which refers to the overall representation of oneself. In the present study, we found that both the posterior and anterior part of the insular cortex are involved in SC. The insular cortex is known to be topographically organized with a degree of complexity increasing along a posterior-anterior axis [8]. Whereas the posterior insular cortex is reported to be involved in processing a variety of bodily sensations and also in higher order somatosensory function, such as the subjective sense of body ownership and agency [39–42], the anterior insular cortex contains the representations of bodily reactions in response to affective feeling states (i.e., somatic markers) [43], sustains visual self-recognition [44, 45], and is involved in metacognitive processes [46]. Considering the involvement of the posterior insular cortex, our results suggest that this region supports conceptual aspects of the self, in addition to the most elementary aspects of subjective sense

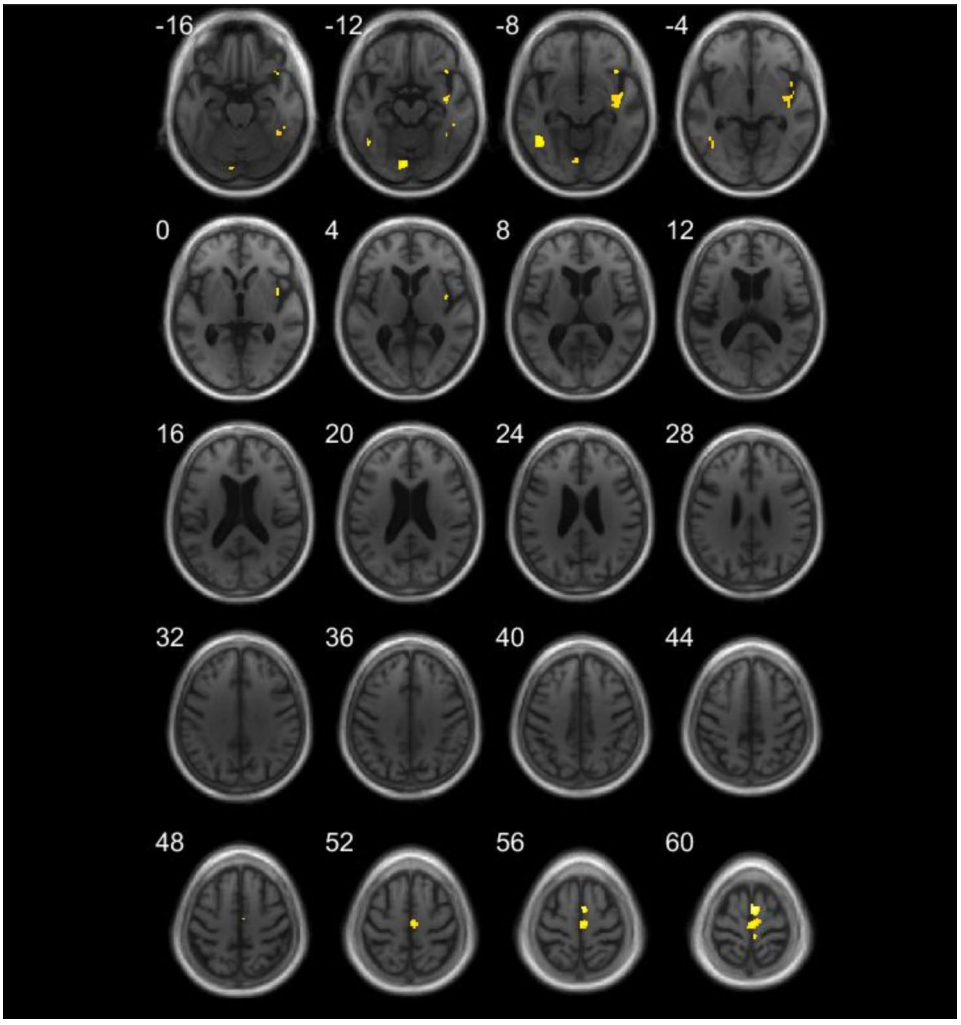

Fig. 3 VBM analyses for self-concept in the Lewy bodies group. Grey matter volumes within right insular cortex, right SMA, bilateral inferior temporal gyri, and left lingual gyrus positively correlated with the total score on the TST questionnaire, using a threshold of $p = .001$ uncorrected, including age, TIV, and MMSE score as nuisance covariates, $k = 50$

Table 2 VBM results for the total score on the Twenty Statements Test in the Lewy bodies group

VBM	Side	BA	k	X	y	z	T
Posterior insula	R	13/21/22	91/333	45	-4.5	-6	3.92
Anterior insula	R	47	35/64	39	19.5	-12	4.3
Supplementary motor area	R	6	506/599	3	-3	58.5	6.43
Fusiform gyrus	R	37	133/185	48	-45	-22.5	4.7
Inferior frontal gyrus	R	47	64/64	40.5	18	-16.5	4.29
Lingual gyrus	L	18	155/160	-7.5	-81	-13.5	4.55
Inferior temporal gyrus	L	37	107/207	-43.5	-64.5	-3	3.92

L left, *R* right, *BA* Brodmann area, *k* cluster size in voxels (specific region's volume/cluster's global volume), x, y, z Talairach coordinates, T T-value

of self. One could hypothesize that the alteration of the subjective sense of self could lead to impairments of the other high order self-components such as SC, through a global collapse of the self. We posit that such damage could disrupt the feeling of what belongs to the self or to the non-self, thus making difficult the access to specific knowledge about the self. Nevertheless, since we did not focus on the subjective sense of self in the present work, our study does not confirm this hypothesis. However, it is concordant with the fact that hypoperfusion in the insula has been associated with Capgras syndrome in DLB [47], which consists of the loss of familiarity toward relatives, who are logically integrated by extension in one's self. Concerning the anterior insular cortex, based on its role

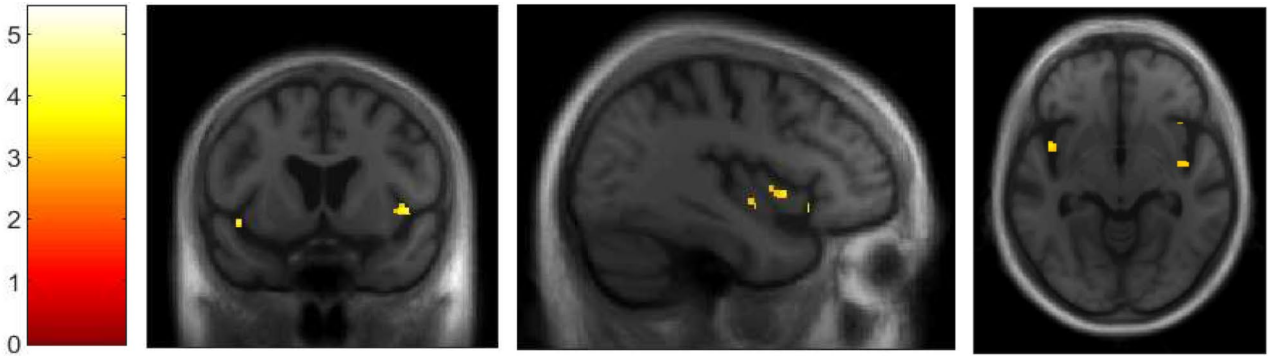

Fig. 4 VBM analyses for self-concept in Lewy bodies group, using a mask for the insula.Grey matter volumes within bilateral insular cortex, using a threshold of $p = .005$ uncorrected, including age, TIV, and MMSE score as nuisance covariates

in self representations [10, 22, 38] and its involvement in metacognition [48], it appears as a main region in the conceptualization of the self. Thus, dysfunction of the anterior insular cortex could disturb the conception we have built of who we are and therefore reduce the ability to answer the question "who am I ?".

Our second main finding concerns the relationship between CMS and the SC. In line with previous studies [49–51], we found that self-referential processes are associated with medial cortical regions, notably the right SMA. The SMA is not classically associated with the CMS as described by Georg Northoff. This area is responsible for planning of complex movements [52] and would sustain the sense of agency [53]. The SMA is well known to entail mirror neurons [54], described in the context of social cognition, rather than in self-cognition. Indeed, mirror neurons are visuomotor neurons discharging when we are executing a motor act or when we observe someone executing a similar motor act [55, 56]. Based on similar mechanisms, the mirror neuron system fires for feelings, such as empathy [57], and is considered to underlie theory of mind [58], which is the ability to infer and reason about another person's mental states [59]. Theory of mind would be based on areas involved in the self brain network, such as the MPFC and the precuneus, and could be supported by representations of the self [60, 61]. Yet, the self-component associated with the SMA would rather pertain to the domain of the subjective sense of self, notably the sense of agency (e.g., when initiating a movement), whereas our study focuses on the conceptual representations of the self. From the perspective of embodied cognition, we can hypothesize that such a region able to simulate our motricity could also support high-order representations of the physical self, actually pertaining to the SC. These findings illustrate the concept of embodied cognition, as described by Binder and Desai for general semantic memory [62]. Indeed, the authors demonstrated that modality-specific systems are recruited when integrating supramodal representations, depending on the categories of representation (e.g. action words referring to face, arm, or leg activate frontocentral motor areas according to a somatotopic organization [63]). Concordant with this hypothesis, it has been demonstrated that mirror-neuron areas are engaged in tasks of self-face recognition [64] and would enable physical other-to-self mapping [65]. Thus, these specific neurons could play a major role in identification and representation of the physical self, which is part of the SC.

Aside from the involvement of insula and CMS, we also found correlations between impairments of the SC and diminished grey matter volume in bilateral inferior temporal gyri – including right fusiform gyrus –, left lingual gyrus and right inferior frontal gyrus. Interestingly, it has been proposed that the inferior temporal gyri, notably the anterior part, might play a key role in semantic memory [66]. In our study, we found correlations in the posterior part, in LB patients, which could be associated with the personal aspects of semantic knowledge. More specifically, the right fusiform gyrus is known to be specialized in face perception [67, 68]. Additionally, Kircher et al. found involvement of the left fusiform gyrus in personality-traits describing the self and perception of own face [45], suggesting a strong involvement of this region in self-processing. Regarding the lingual gyrus, it is a region essential for visual perception [69] and visual memory [70]. Likewise, the lingual gyrus plays a central role in divergent thinking [71], which refers to the processes allowing one to generate creative ideas by exploring different possibilities. We could speculate that divergent thinking is involved in the creation of oneself prototype. Interestingly, we found diminished grey matter volume in the right inferior frontal gyrus, which has been related to verbal fluency [72]. Yet, the TST score and verbal fluency were positively correlated in our study and could reflect research strategies in memory. Another ability that is necessary to describe one's own SC is introspection, which has been associated with inferior frontal gyrus by means of multiband functional MRI during

structured real-time conversations, in which the participant verbalized introspected thought and feeling [73]. Impairments in self-introspection could explain a poorer SC, and even be linked to impairments in introspection of consciousness, related to anosognosia. Indeed, introspection is closely linked to metacognition which is part of the subjective sense of self [18]. Subjective sense of self and SC are two interrelated concepts and distinguishing between them represents a real experimental challenge.

Overall, our study has some limitations. First, the sample sizes were relatively small ($N=20$ in each group) with a high number of covariates and the results for the VBM analyses were uncorrected. These preliminary results should therefore be interpreted carefully and be confirmed with additional studies, involving a larger cohort of DLB patients. Moreover, comparing the SC across different clinical populations (e.g. fronto-temporal lobar degeneration, AD) at the same stage would highlight the impact of different neurodegenerative processes on the SC. Second, it would have been useful to assess and integrate other components of the self, such as subjective sense of self and autobiographical semantic memory, as additional covariates, in order to better isolate the SC. Therefore, our future work aims to investigate the relationship between the subjective sense of self, the SC, and autobiographical memory in both DLB and AD, with a special focus on the insula's role within the different components.

Conclusions

Our work on the SC in DLB has both clinical and theoretical interest. First, it is the first study to demonstrate the existence of SC impairments in LB patients. Concordant with our hypothesis, these difficulties are related to insular atrophy, which occurs early in the course of the disease. Moreover, our study confirms the involvement of the SMA in the self, and notably suggest a role for mirror neurons. Finally, we found that bilateral inferior temporal gyri, right inferior frontal gyrus and left lingual gyrus also play a role in the SC. This finding brings new insights regarding the implication of the insula in the different aspects of the self. Our results show that the SC relies on the insula and other brain regions involved in the other components of the self, such as the subjective sense of self. These findings suggest that conceptual representations of the self could arise from the primary phenomenological levels.

Abbreviations

DLB	Dementia with Lewy bodies
LB	Lewy bodies
SC	Self-concept
MRI	Magnetic resonance imaging
AD	Alzheimer's disease
CMS	Cortical midline structures
SMA	Supplementary motor area
SD	Standard deviation
DAT	Dopamine transporter SPECT
CSF	Cerebrospinal fluid
MMSE	Mini-Mental State Examination
RBD	Rapid eye movement sleep behavior disorder
TST	Twenty Statements Test
VBM	Voxel-based morphometry
GM	Grey matter
FDR	False discovery rate
TIV	Total intracranial volume

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-024-01447-2.

Supplementary Material 1

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Author contributions

Study conception and design (N.P., F.B., A.T.) and study coordination (N.P., F.B., A.T., A.B.); acquisition of clinical data (A.T., N.P., F.B., C.M., H.D., C.D., A.R.); acquisition of MRI data (A.T., P. L. S.); extraction of clinical data (L.S.); manuscript preparation (A.T., N.P.); critical revision of the manuscript (N.P., F.B.); imaging and statistical analysis (A.T., M.M.). All authors reviewed and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The local ethics committee approved the study protocol ("Comité de Protection des Personnes Sud Méditerranée III"; approval number 2020-A02475-34). All participants provided written informed consent.

Consent for publication

Not applicable.

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Publisher's Note

4. Étude de la mémoire autobiographique épisodique dans la MCL

Neuroimagerie de la mémoire autobiographique dans la MCL : une histoire d'insula

Après avoir caractérisé les déficits du sens subjectif et de soi et du self-conceptuel dans la MCL, nous nous sommes intéressés à la composante du self entendue dans le temps : la mémoire autobiographique, avec un regard comportemental et en neuroimagerie. La mémoire autobiographique renvoie aux expériences personnellement vécues et aux connaissances autobiographiques, contribuant à la construction des représentations de soi à travers le temps. La mémoire autobiographique distingue un versant épisodique, et un versant sémantique. Dans cette étude, nous avons analysé les aspects épisodiques de la mémoire autobiographique, qui renvoient au sens subjectif de soi projeté dans l'expérience passée, qui est rattachée à un lieu et à un moment précis, qui est teintée d'émotions et enrichie par des détails perceptuels. La composante sémantique, quant à elle, fait référence aux résumés de vie dépourvus de contexte spatio-temporel précis et aux connaissances en lien avec notre vie personnelle passée. La composante sémantique ne sera pas abordée dans la présente section. Du point de vue anatomique, la mémoire autobiographique repose sur un réseau de régions cérébrales bien identifié, comprenant notamment les régions temporales internes et latérales, les régions préfrontales médianes, les régions pariétales postérieures et le cervelet. Certaines études ont également mis en évidence un rôle pour l'insula (Descamps et al., 2021; Fink et al., 1996).

Alors que les troubles de la mémoire autobiographique sont considérés comme un marqueur « transdiagnostique » des maladies neuroévolutives cognitives (Irish, 2023), ils n'avaient jusqu'alors, jamais été caractérisés dans la MCL. Dans cette étude, nous avons, au moyen de l'AI, étudié la mémoire autobiographique dans la MCL, à travers cinq périodes de vie, et selon une condition de « rappel libre » et une condition d'« indiçage spécifique ». Les résultats ont été comparés entre les patients atteints de MCL et les sujets témoins, et des corrélations en imagerie volumétrique ont été menées dans le groupe MCL.

Nous avons fait l'hypothèse d'une atteinte de la mémoire autobiographique, non graduée dans le temps, en lien avec l'altération globale du self. De plus, étant donné qu'il existe, dans la MCL, des troubles de la mémoire caractérisés par un déficit prédominant sur la récupération des informations (Kemp et al., 2017), nous avons supposé que le groupe de patients

bénéficierait d'une amélioration de la richesse épisodique, dans la condition d'indiçage spécifique. Enfin, par le lien étroit entre le self et l'insula, nous avons supposé qu'il existerait des corrélations entre la mémoire autobiographique et le cortex insulaire.

BRAIN COMMUNICATIONS

Neuroimaging of autobiographical memory in dementia with Lewy bodies: a story of insula

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Although deficits in learning and retrieving new information are well characterized in dementia with Lewy bodies, autobiographical memory has never been explored in this disease. Yet, autobiographical memory impairments are a pervasive feature of dementia, well characterized in other neurodegenerative diseases. Moreover, autobiographical memory corresponds to an extension over time of the self, which we hypothesize is altered in dementia with Lewy bodies and impairment of which could be linked to the insular atrophy occurring from an early stage of the disease. In this study, we sought to characterize autobiographical memory impairments and explore their neural correlates in dementia with Lewy bodies, on the assumption that insular damage could impact the self, including its most elaborate components, such as autobiographical memory. Twenty patients with prodromal to mild dementia with Lewy bodies were selected to participate in this exploratory study along with 20 healthy control subjects. The Autobiographical Interview was used to assess autobiographical memory. Performances were compared between patients and control subjects, and an analysis across life periods and recall conditions was performed. 3D magnetic resonance images were acquired for all participants, and correlational analyses were performed in the patient group using voxel-based morphometry. The behavioural results of the Autobiographical Interview showed that autobiographical memory performances were significantly impaired in dementia with Lewy body patients compared to control subjects in a temporally ungraded manner, for both the free recall and the specific probe conditions ($P < 0.0001$), though with greater improvement after probing in the patient group. Furthermore, autobiographical memory impairments were correlated with grey matter volume within right insular cortex, temporoparietal junction, precuneus, putamen, left temporal cortex, bilateral parahippocampus and cerebellum, using a threshold of $P = 0.005$ uncorrected. The behavioural results confirm the existence of temporally ungraded autobiographical memory impairments in dementia with Lewy bodies, from the early stage of the disease. As we expected, neuroimaging analysis revealed a role for the insula and the precuneus in autobiographical memory retrieval, two regions associated with elementary aspects of the self, among other brain regions classically associated with autobiographical memory, such as medial temporal lobe and temporoparietal junction. Our findings provide important insights regarding the involvement of the insula in the self and suggest that insular damage could lead to a global collapse of the self, including its more elaborated components, such as autobiographical memory.

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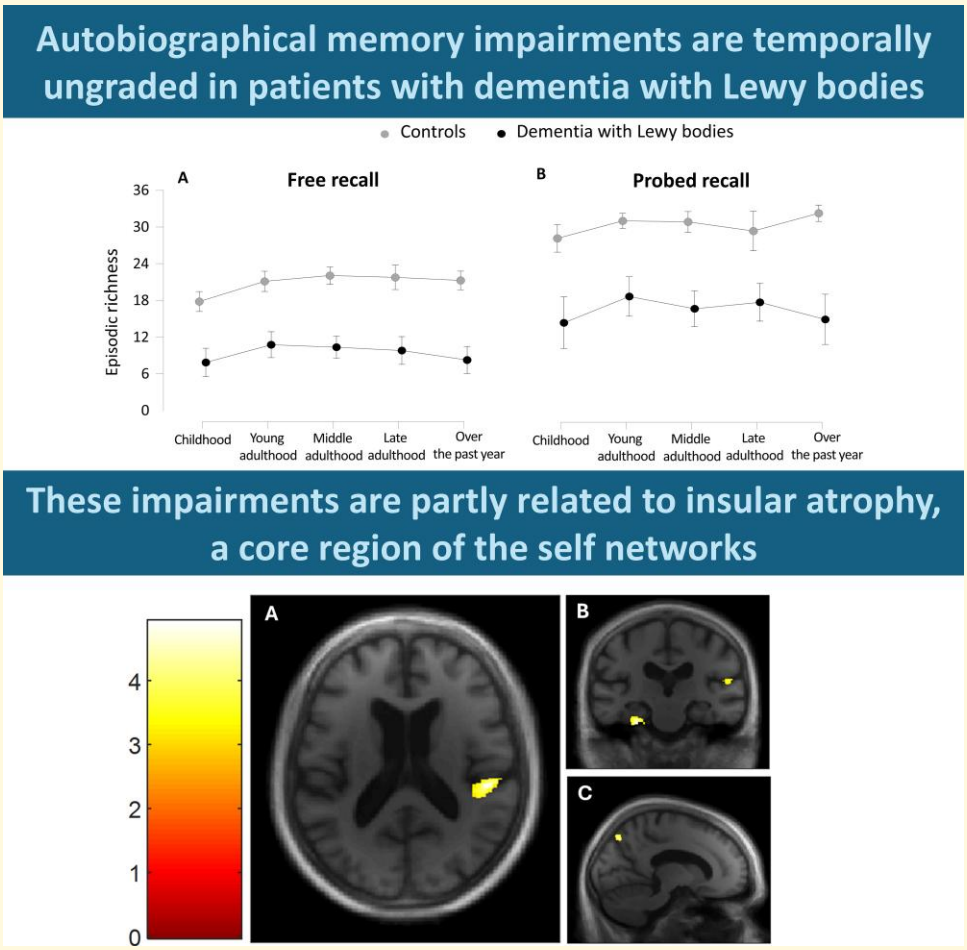
Graphical Abstract



Introduction

While pervasive deficits in learning and retrieving new information are well characterized in dementia with Lewy bodies,[1,2] autobiographical memory (ABM) has never been explored in this disease. Yet, in dementia with Lewy bodies, there seem to be obvious alterations of the present self,[3-7] which has been proposed as a prerequisite for the self extended in time, namely ABM.[8-10] The present self pertains to the aspects of the sense of self that are related to and accessible in the present moment. According to Prebble *et al.*,[9] the present self comprises two components: the subjective sense of self and the self-concept. The subjective sense of self refers to the subjective living experience that implies the construction of a mental representation,[11-13] whereas the self-concept contains the object of this representation, including knowledge about ourselves.[12,14] Recently, a study in dementia with Lewy body patients has shown deficits in awareness, such as anosognosia[3] that could reflect alteration of the subjective sense of self, while other studies demonstrated that dementia with Lewy body patients display changes in their personal tastes and impairments in representing who they are,[5,15] revealing alteration of the self-concept. In these latter studies, we were able to link the alteration of the self to the insula, which is damaged early in the course of dementia with Lewy bodies[16-19] and is a core region for the self.[15] Indeed, the insula is involved in multiple processes related to the present self, ranging from internal bodily states, such as interoception,[20,21] to high-order processes, such as knowledge about oneself,[7,22] but little is known about its contribution to the self extended in time.

ABM refers to the capacity to recollect experiences personally lived and to autobiographical knowledge, supporting the construction of the representation of our identity over time.[23] ABM is a complex construct that can be dissected into two distinct memory systems: an episodic one and a semantic one.[10,24] The episodic component refers to the subjective re-experiencing of events from the past, with emotions and perceptual details, within a particular place and

time, whereas the semantic components consist of knowledge, facts and conceptual information related to personal life, devoid of the spatio-temporal context in which this information was acquired.[25] However, an obvious interconnection between the self and ABM is recognized by expert researchers in the field.[8,9,21,26,27] A growing number of studies have investigated the neurobiological basis of this complex form of cognition. In a meta-analysis conducted using haemodynamic imaging in healthy adults,[28] researchers identified a core ABM network, comprising medial temporal lobe structures, including the hippocampus and parahippocampal cortices, the lateral temporal cortices, the medial prefrontal, posterior parietal region and the cerebellum, whereas the lateral prefrontal and temporal cortices, insula, precuneus and basal ganglia appeared less frequently involved. To our knowledge, only two studies found a correlation between the insula and ABM. In the first study, Fink *et al.*[29] found the insula to be a secondary region of ABM in a healthy population. In the second study, Descamps *et al.*[30] found a diminished ABM richness in patients with insular resection compared to healthy controls. Moreover, some behavioural studies found impaired ABM in disorders associated with insular dysfunction, such as schizophrenia and autism spectrum disorders,[31,32] though no imaging study to confirm potential insular involvement was included.

Impaired ability to remember events from the past is considered a transdiagnostic feature of dementia and is often among the earliest symptoms reported by patients. ABM impairments can take different forms arising from the dysfunction of neurocognitive processes, depending on the distribution of neural atrophy in the brain.[33] In Alzheimer's disease, episodic memory dysfunction caused by neuronal degeneration in the medial temporal lobe leads to an extended retrieval deficit due to a global degradation of specific ABM,[34,35] more pronounced for the recent period due to an additional encoding/consolidation deficit for recent memories.[36,37] Meanwhile, semanticized memories from remote periods of life are better preserved given that they rely on the relative integrity of the temporal neocortex.[38] Conversely, semantic dementia is characterized by damage to the anterior temporal neocortex[39] and by a 'reversed' ABM profile, with spared recent episodic memories[40] contrasting with the loss of remote semanticized memories.[35,41] In the behavioural variant of frontotemporal dementia, which is characterized by damage to the frontoinsular and ventromedial prefrontal cortices,[42,43] the ABM profile appears flat due to multiple mechanisms, including strategic retrieval difficulties.[33,35,40,44] A similar ABM flat profile is described in posterior cortical atrophy and would be related to disruption of access to the visual contextual information integral to the ABM trace, in connection with atrophy of posterior parietal regions, including the right précuneus.[45]

Despite the evidence of altered ABM in the aforementioned dementia syndromes, no studies have yet explored this type of memory in dementia with Lewy bodies, which is, however, the second most common form of cognitive neurodegenerative disease after Alzheimer's disease.[46,47] Thus, in this paper, we report the first behavioural and neuroimaging study of ABM in dementia with Lewy body patients. Our purpose was to explore the potential ABM deficit in dementia with Lewy bodies along with its anatomical substrates, with a particular interest in the insula. Based on the premise that the insula is damaged at an early stage in dementia with Lewy body patients and based on the assumption that the insula plays a central role in the self, we predicted that ABM would be impaired in an ungraded manner due to a global alteration of the self. Moreover, given that memory disorders in dementia with Lewy bodies are characterized by deficits in learning and retrieving the information, we expected that retrieval support would have beneficial effects on the richness of memories.

Materials and methods

Study population

The current study was conducted using the same cohort of patients as in our previous research on the self.[6] Specifically, it included 20 patients with early-stage dementia with Lewy bodies and 20 healthy control subjects matched for age, gender and level of education (with a minimum of 9 years) were enrolled in the present study between January 2021 and February 2023. Patients were recruited from the tertiary memory clinic of Strasbourg University Hospital (CM2R of Strasbourg), France, including the geriatrics and neurology departments. Control subjects were recruited in three ways: among friends and relatives of the patients, via the listing of controls of the local clinical investigation centre and from the control group of the AlphaLewyMA cohort (http://clinicaltrials.gov/ct2/show/NCT01876459). Diagnosis of prodromal and mild dementia with Lewy bodies was based on core clinical features.[48,49] Some of the patients had also benefited from biomarkers during their clinical follow-up. Indeed, a dopamine transporter (DAT) imaging was performed when parkinsonism was doubtful, and a CSF analysis was performed when an amnestic syndrome of hippocampal type suggested possible Alzheimer's disease, to ensure that there was no co-pathology. Thus, a DAT scan was available to support the diagnosis in approximately a quarter of the patients, and CSF analysis was available to confirm the absence of associated Alzheimer's disease in approximately half of the patients. Patients with prodromal dementia with Lewy bodies were defined as having mild cognitive impairment if they had a Mini-Mental State Examination (MMSE) score of ≥26, had preservation of independence as assessed by the Instrumental Activities of Daily Living[50] and fulfilled both the DSM-5 criteria of mild neurocognitive disorder[51] and McKeith's criteria for the diagnosis of prodromal dementia with Lewy bodies.[48] Patients were defined as having mild dementia with Lewy bodies if they had an MMSE score between 20 and 25 and were diagnosed as having probable dementia with Lewy bodies according to the current dementia with Lewy body criteria.[49] All participants benefited from a classic medical examination, which notably included evaluation of the features of parkinsonism using the Unified Parkinson's Disease Rating Scale (Part 3): akinesia, rigidity and resting

tremor (rated from 0 for no symptoms to 4 for serious symptoms). The dementia with Lewy bodies group underwent further clinical examination of dementia with Lewy body core criteria, among which fluctuations were assessed with the Mayo Clinic Fluctuations Scale[52] and the Newcastle-upon-Tyne Clinician Assessment of Fluctuation Scale.[53] The Parkinson's disease-associated psychotic symptoms questionnaire[54] was used to evaluate the presence of hallucinations. Rapid eye movement sleep behaviour disorder (RBD) was evaluated using a sleep questionnaire on RBD,[55] simplified into four questions, two each for the patient and for the caregiver: one concerning movements during sleep and the second concerning vivid dreams and nightmares.

Subjects with a history of alcohol/substance abuse, significant visual or auditory disabilities, relevant neurological of psychiatric comorbidities or the presence of other severe or unstable medical illnesses were not enrolled in the study. Subjects with an abnormal neurological examination—except for parkinsonism in the case of patients—depression symptoms (mini-Geriatric Depression Scale[56]) or a significant cerebral vascular burden (Modified Hachinski Ischemic Score of >7[57]) were not enrolled. Participants with CSF biomarkers suggestive of Alzheimer's disease (i.e. abnormal Aβ42/Aβ40 ratio, t-Tau, phospho-Tau181) were not enrolled. Finally, participants with claustrophobia or contraindications to MRI were not enrolled. All participants provided written informed consent for the study, in accordance with the Declaration of Helsinki, and the study was approved by the ethics committee Sud Méditerranée III.

Behavioural study

Baseline

General cognitive assessment was performed in the patients, including an evaluation of anterograde memory with the RL/RI-16 ('Rappel libre/Rappel indicé à 16 items', i.e. 16-item free recall/probed recall),[58] a French test similar to the FCSRT (Free and Cued Selective Reminding Test),[59] verbal fluencies,[60] Frontal Assessment Battery,[61] TMTA and TMTB,[62] digit span of the WAIS (Wechsler Adult Intelligence Scale)[63] and Rey-Osterrieth Complex Figure.[64] The results are displayed in Supplementary Table 1.

Autobiographical Interview

The Autobiographical Interview[25] was administered and rated according to Levine's methodology,[65] for an analysis of the participants ability to relate, under different levels of retrieval support, autobiographical memories established at different times in their lives. Participants were instructed to provide detailed descriptions of two events that were personally experienced and that occurred at a specific time and place from each of five life periods (childhood, age 0–15 years; young adulthood, age 16–30; middle adulthood, age 31–50; late adulthood, age 51–the past year; during the past year). In the original version of the Autobiographical Interview,[25] only one event per life period was required, but in the present study, participants were asked to describe two events, so as to increase the quantity of material to be analysed. Life periods were randomly assigned during the session, and a list of 20 word cues (e.g. car, piano, apple) was presented to assist in event retrieval.

To examine facilitative effects of retrieval support on memory, we manipulated the level of structure available to participants across three conditions: free recall, general probe and specific probe. At free recall, participants spoke about the event without any interruption from the examiner, continuing until they had reached a natural ending point. After an event had been recalled, the examiner prompted the participant once for a greater recall of details (general probe). At the specific probe phase, a structured interview was administered to elicit additional contextual details encompassing four categories: time, place, perceptual details and emotion/thought.

Descriptions were recorded and transcribed. Following administration, event descriptions were segmented into details and classified as 'internal' and assigned to one of five categories (event, place, time, perceptual and emotion/thought) if they related directly to the main event described, were specific to time and place and conveyed a sense of episodic re-experiencing. Otherwise, details were considered 'external', consisting of satellite autobiographical events or unrelated to the main event, semantic facts, repetitions or other metacognitive statements. Details from each category were summed separately for each condition (i.e. free recall, general probe, specific probe). As the effect of general probing on general performance is minimal in comparison to that of specific probing,[25] free recall and general probe scores were combined. Quantitative ratings were accompanied by qualitative ratings assigned for time, place, perception and emotion/thought, with the possibility of attaining a maximum rating of 3 points for each category (time, place, perceptual, emotion/thought). A rating of 3 points was assigned when the description was rich, highly specific and appeared to emerge from a feeling of re-experiencing. A rating of 2 points was assigned to detailed descriptions falling short of a 3-point description. A rating of 1 point was assigned to descriptions containing general, non-specific information but still episodic in nature. A rating of 0 point was assigned when there was no information pertaining to the specified category, or for responses based on semantic knowledge rather than episodic memory. Episodic richness (the overall degree to which a feeling of re-experiencing was conveyed) was rated on a similar scale that was extended to 6 points to provide a more accurate rating and to take into account the greater importance of this category relative to the others. Although ratings in the first four categories were mutually exclusive (i.e. aspects of a memory could not be counted in more than one category), the episodic richness was based on an overall assessment of the event. To investigate potential differences across time periods, the episodic richness ratings of the two memories were added for each period for both the free recall (i.e. free recall plus general probe) and the probed recall (i.e. total score following probing) (maximum = 36). To analyse the possible differences between the two recall conditions, the scores of each period were added up to obtain a general free recall score and probed recall score (maximum = 180).

Participants' memories were scored by one trained rater (A.T.). To assess interrater reliability, 10% of the memories

were selected at random (with the constraint that age, groups and life periods were equally represented) and scored by another trained rater (N.P.) who was blind to subject status, in accordance with established scoring procedures from previous research.[25,66] Interrater reliability was high for free recall score and probed recall score (all Cronbach's $\alpha \geq 0.94$).

Statistical analysis for the behavioural study

Student's *t*-tests were used to compare intergroup differences between dementia with Lewy body patients and control subjects for demographic quantitative data. A χ^2 test was used to compare the sex ratio between groups. For the behavioural data, Mann–Whitney U-tests were used to compare the free recall score and probed recall score,[25] for both dementia with Lewy body patients and control subjects, as we hypothesized that scores would be lower in the free recall condition compared to the specific probe. We also compared the percentage of improvement after specific probe ((probed recall score-free recall score/free recall score) × 100) between dementia with Lewy body patients and control subjects, using Mann–Whitney U-tests. Two-way repeated measures ANOVAs, including age as nuisance covariate, were conducted to examine the effect of life period across the different recall conditions, for both dementia with Lewy body patients and control subjects. Bonferroni correction was applied for multiple comparisons.

Neuroimaging study

As described previously,[6] each participant underwent a high-resolution anatomical MRI scan within a maximum of 12 weeks after taking the Autobiographical Interview. T_1-weighted 3D anatomical images were obtained using a 3T MRI scanner (Verio 32-channel Tim Siemens scanner; Siemens, Erlangen, Germany) using a volumetric magnetization-prepared rapid acquisition with gradient-echo (MPRAGE) sequence (field of view = 256 × 256 mm, image matrix = 256 × 256, slice thickness = 1 mm, repetition time = 1900 ms, echo time = 2.52 ms, flip angle = 9°).

Voxel-based morphometry analyses

We used voxel-based morphometry (VBM) to investigate differences in grey matter (GM) volume between the healthy controls and the dementia with Lewy body patients and to examine the neuroanatomical correlates of ABM in dementia with Lewy body patients. VBM analyses included image preprocessing and statistical analyses. These steps were carried out using the SPM12 software package (Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/) running on Matlab R2017b (MathWorks, Natick, MA, USA). Anatomical MRI images were spatially preprocessed using standard procedures.[67] All T_1-weighted structural images were first segmented, bias corrected and spatially normalized to the Montreal Neurological Institute space using an extension of the unified segmentation procedure that includes six classes of tissue.[68] The DARTEL registration toolbox was then used to build a study-specific template and to bring into alignment all of the segmentation images. The VBM analysis was done on modulated GM images; that is, the GM value in each voxel was multiplied by the Jacobian determinant derived from the spatial normalization. This procedure preserves the total amount of GM from the original images. These modulated GM images were smoothed with a Gaussian kernel (full width at half maximum: 8 mm). Between-group voxel-based comparisons were displayed after correcting for multiple comparisons with false discovery rate (FDR; $P < 0.05$). A voxel-wise general linear model was employed to investigate the regions of atrophy related to disorders of the episodic ABM, in dementia with Lewy body patients. To analyse the potential different regions involved in the free recall and in the probed recall, we tested the correlation between the GM volume and both the free recall score and the probed recall score, using a threshold of $P = 0.005$ uncorrected, including age, gender and total intracranial volume (TIV) as nuisance covariates. MMSE was also considered as an additional covariate to investigate the potential impact of disease severity. Moreover, to obtain a control measure of memory not involving the self, we tested the correlations between GM volume and the 1–3 free and total recall conditions of the RL/RI-16,[58] using the same threshold, including the same nuisance covariates as for the Autobiographical Interview. A cluster spatial extent of 50 voxels was used to avoid irrelevant and isolated detections. The software xjView (http://www.alivelearn.net/xjview8/) enabled us to characterize each cluster.

Results

Clinical characteristics

Twenty patients with early-stage dementia with Lewy bodies and 20 healthy control subjects were enrolled in the present study. A description of the study population is presented in Table 1. Groups were well matched for age ($t = 0.64$, $P = 0.526$), years of education ($t = -1.61$, $P = 0.116$) and sex ($\chi^2 = 0.44$, $P = 0.507$). The dementia with Lewy bodies group comprised 13 patients at the prodromal stage of dementia with Lewy bodies and 7 patients at the mild stage of the disease. Among the 20 dementia with Lewy body patients, 85% presented fluctuations, 60% presented hallucinations or illusions and 60% presented RBD. Concerning parkinsonism features, akinesia was observed in 80% of dementia with Lewy body patients, rigidity in 70% of dementia with Lewy body patients and resting tremor in only one patient (5%).

Behavioural study

Overall performance on the Autobiographical Interview

Figure 1 shows the total scores of episodic richness summed across all time periods in the free and probed retrieval

Table 1 Demographic and clinical characteristics of the dementia with Lewy bodies group and the control group

Characteristic	Dementia with Lewy bodies group ($n = 20$)	Control group ($n = 20$)	Student's t-test or χ^2 test
Mean age in years (+SD)	71.9 (7.9)	70.4 (7.3)	$t = 0.64$, $P = 0.526$
Years of education (+SD)	12.7 (2.5)	14.05 (2.6)	$t = -1.61$, $P = 0.116$
Sex, M/F	14/6	12/8	$\chi^2 = 0.44$, $P = 0.507$
MMSE score (/30)	26.3 (2.39)	28.8 (1.0)	$t = -4.32$, $P < 0.001$
Handedness, R/L	19/1	20/0	$\chi^2 = 1.03$, $P = 0.311$
Mean of disease duration (+SD)	3.19 (2.12)	N/A	
Fluctuations (%)	17/20 (85)	N/A	
Hallucinations/illusions (%)	12/20 (60)	N/A	
RBD (%)	12/20 (60)	N/A	
Parkinsonism			
Akinesia (%)	16/20 (80)	N/A	
Rigidity (%)	14/20 (70)	N/A	
Tremor at rest (%)	1/20 (5)	N/A	

Significant *P*-value and χ^2 value are in italics. SD, standard deviation; M, male; F, female; MMSE, Mini-Mental State Examination; R, right; L, left; RBD, rapid eye movement sleep behaviour disorder; N/A, not applicable.

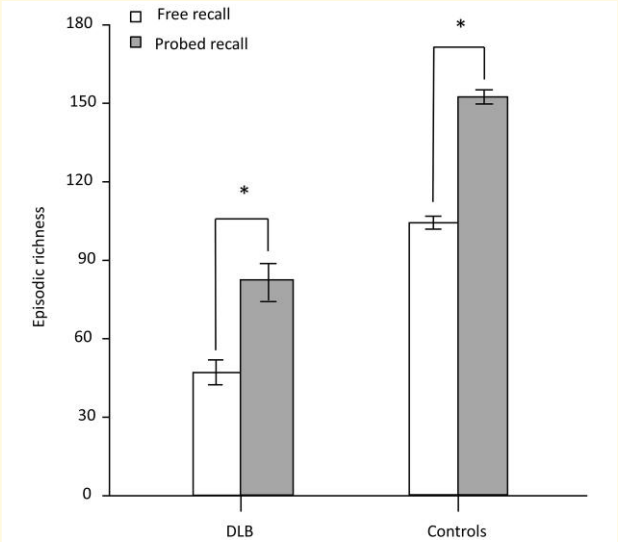


Figure 1 Total scores of episodic richness for the free recall and probed recall on the Autobiographical Interview, for all participants. Mann–Whitney U-tests were used to compare the free recall score and probed recall score for both dementia with Lewy body patients ($n = 20$) and control subjects ($n = 20$). *$P < 0.0001$ (error bars represent standard deviation). DLB, dementia with Lewy bodies.

conditions of the Autobiographical Interview. Mann–Whitney U-test revealed that controls displayed higher episodic richness across both retrieval conditions in comparison to dementia with Lewy body patients ($P < 0.0001$). The mean score obtained in free recall was significantly inferior in the dementia with Lewy bodies group (46.9, SD 21.02) than in the control group (103.95 SD 11.17) ($U = 2.5$, $P < 0.0001$). Similarly, the mean score obtained in probed recall was significantly inferior in the dementia with Lewy bodies group (82.3, SD 31.68) than in the control group (152.1, SD 12.36) ($U = 2.5$, $P < 0.0001$). The episodic richness evolution rate between the free recall score and the probed recall score was higher in dementia with Lewy body patients (gain of 75.48% of episodic richness in the probed recall) compared to controls (gain of 46.32% of episodic richness in the probed recall) ($U = 341$, $P < 0.0001$).

ABM retrieval across life periods

Figure 2 shows the profile of free recall and probed recall across life periods. A two-way repeated measures ANOVA revealed significant main effect for group [$F(1,37) = 98.93$, $P < 0.0001$], with controls displaying overall higher episodic richness than dementia with Lewy body patients ($t = 9.95$, $P < 0.001$). Another significant main effect was found for recall condition [$F(1,37) = 9.83$, $P = 0.0034$], with significantly higher episodic richness in the probed recall condition for both dementia with Lewy body patients and controls ($t = -23.23$, $P < 0.001$). There was also a significant interaction between group and recall condition [$F(1,37) = 11.16$, $P = 0.0019$], with significantly lower scores in the dementia with Lewy bodies group compared to the control group for both free recall ($t = 8.62$, $P < 0.001$) and probed recall ($t = 10.48$, $P < 0.001$) conditions. No significant main effect was found for life periods for both controls and dementia with Lewy body patients, in either the free recall condition or the probed recall condition. Other comparisons did not reveal significant differences between the scores.

Neuroimaging study

A voxel-based analysis comparing GM volume in dementia with Lewy body patients versus control subjects is presented in Supplementary Fig. 1. The analysis included TIV and age as nuisance covariates and revealed patterns of cerebral atrophy typically reported in dementia with Lewy body patients,[17,69] with reduction in GM volume in the insular, temporal, occipital, frontal and cingular cortices, and to a lesser extent the parietal cortex, and also in the cerebellum and subcortical regions such as the putamen ($P < 0.05$, FDR corrected), when compared to control subjects.

The free recall score and the probed recall score were analysed separately to examine facilitative effects of retrieval

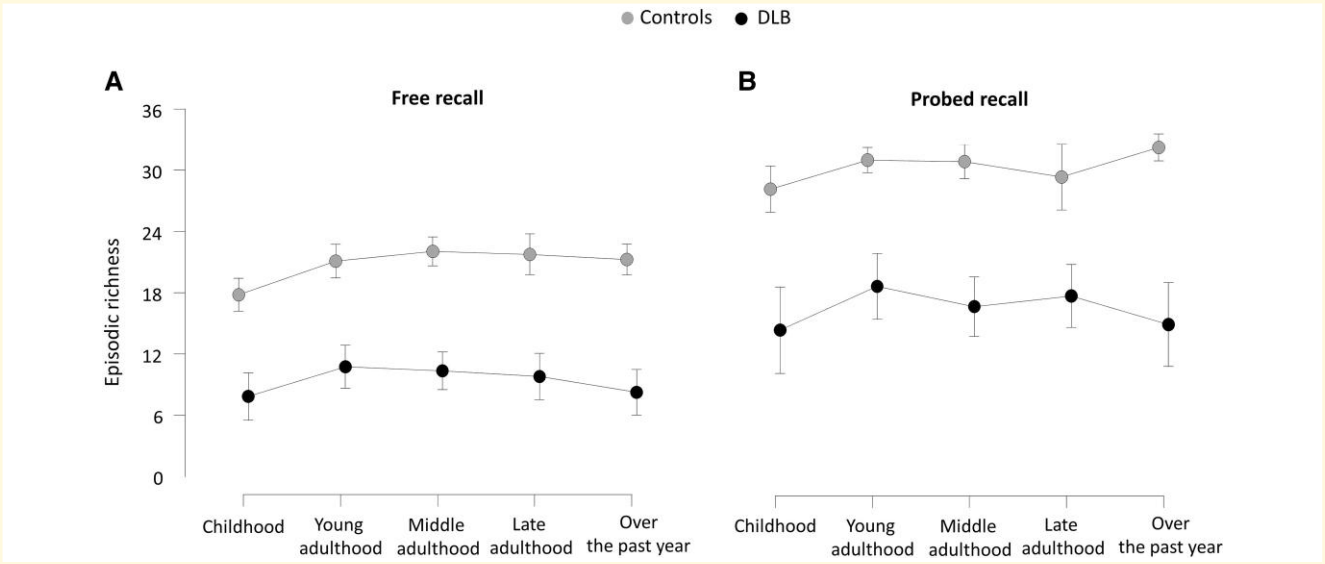


Figure 2 Profile of free recall (A) and probed recall (B) across life periods on the Autobiographical Interview for all participants. Two-way repeated measures ANOVAs, including age as nuisance covariate, were conducted to examine the effect of life period across the different recall conditions, for both dementia with Lewy body patients ($n = 20$) and control subjects ($n = 20$). Bonferroni correction was applied for multiple comparisons (error bars represent standard deviation). DLB, dementia with Lewy bodies.

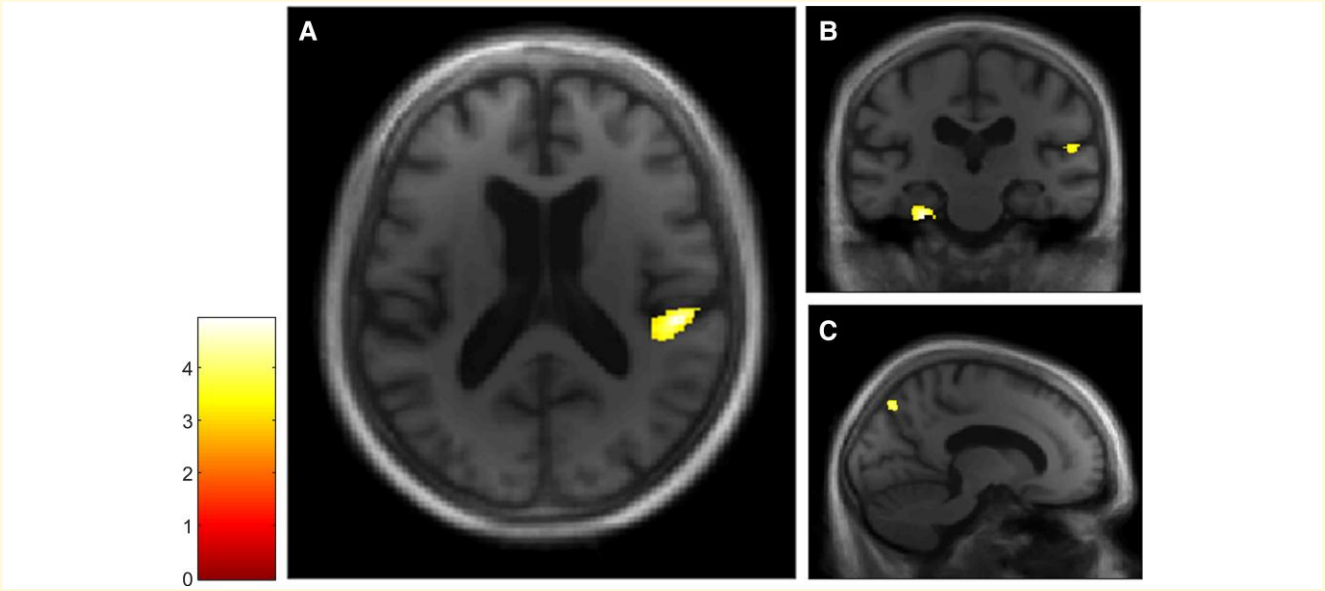


Figure 3 VBM analyses for the Autobiographical Interview free recall condition in the dementia with Lewy bodies group. Multiple linear regression was used to obtain correlation for Autobiographical Interview free recall score and GM volume in patients with dementia with Lewy bodies ($n = 20$). GM volumes within right posterior insula (**A** and **B**), left parahippocampal gyrus and right temporoparietal junction (**B**) and right precuneus (**C**) are positively correlated with the free recall score on the Autobiographical Interview, using a threshold of $P = 0.005$ uncorrected, including age, gender, TIV and MMSE score as nuisance covariates ($k = 50$).

support on memory. VBM analyses revealed a positive correlation between both the free recall score (Fig. 3) and the probed recall score (Fig. 4) and GM volumes within a total of seven clusters, four of which were common to both Autobiographical Interview conditions (see Table 2). The first cluster included the right posterior insular cortex and the temporoparietal junction, the second cluster included the right precuneus, the third cluster included the right parahippocampal gyrus and the fourth cluster included the left parahippocampal gyrus and the left cerebellum. In the free recall condition, other clusters were found in the right cerebellum and in the right putamen, whereas in the probed recall

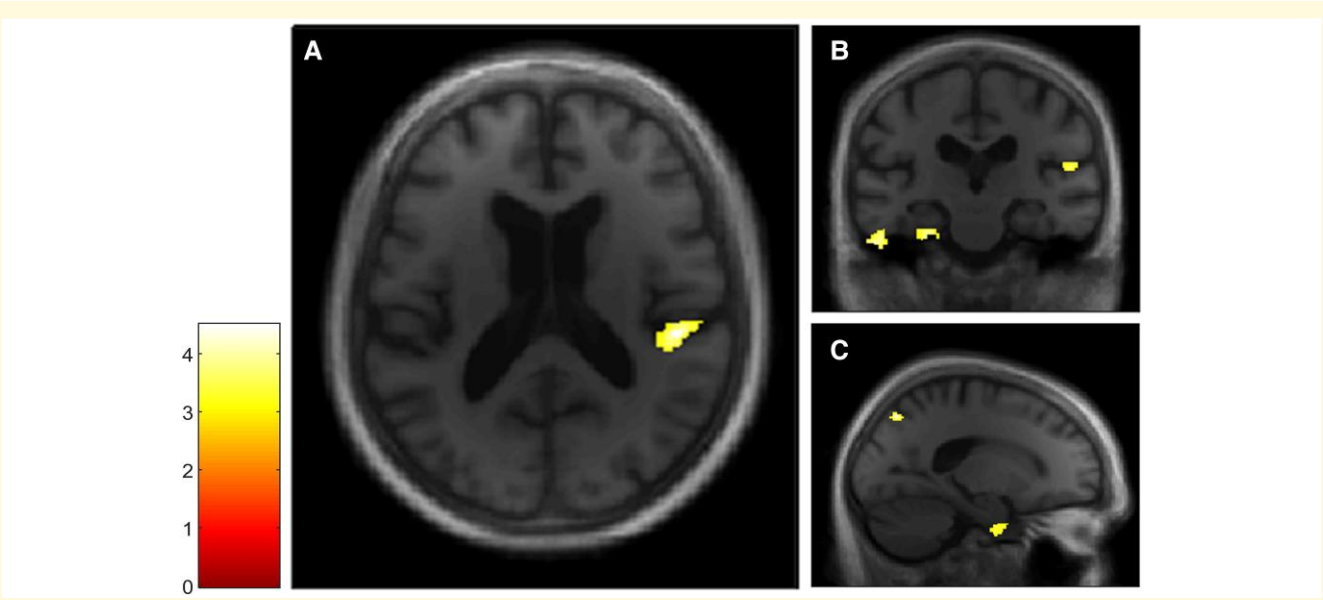


Figure 4 VBM analyses for the Autobiographical Interview probed recall condition in the dementia with Lewy bodies group. Multiple linear regression was used to obtain correlation for Autobiographical Interview probed recall score and GM volume in patients with dementia with Lewy bodies ($n = 20$). GM volumes within right posterior insula (**A** and **B**), left inferior temporal and parahippocampal gyri (**B**) and right precuneus and parahippocampal gyrus (**C**) are positively correlated with the probed recall score on the Autobiographical Interview, using a threshold of $P = 0.005$ uncorrected, including age, gender, TIV and MMSE score as nuisance covariates ($k = 50$).

Table 2 VBM results for the free recall and probed recall conditions on the Autobiographical Interview in the dementia with Lewy bodies group

				K	
Cluster	**VBM**	**Side**	**BA**	**FRS**	**PRS**
1.	Posterior insular cortex	R	13	216/813	226/765
	Temporoparietal junction	R	41	361/813	305/765
2.	Precuneus	R	7	97/112	184/194
3.	Parahippocampal gyrus	R	28/36	120/126	509/544
4.	Parahippocampal gyrus	L	35/36	393/701	423/709
	Cerebellum	L	NA	109/701	104/709
5.	Cerebellum	R	NA	93/100	
6.	Putamen	R	NA	92/195	
7.	Inferior temporal gyrus	L	20		77/137

Please note that the entire table with exact Talairach coordinates is provided in Supplementary Table 2. FRS, free recall score; PRS, probed recall score; L, left; R, right; BA, Brodmann area; *K*, cluster size in voxels (specific region's volume/cluster's global volume).

condition, another cluster was found in the left inferior temporal gyrus.

VBM analyses for both the 1–3 free and total recall at the RL/RI-16 did not reveal any association with the insula. The results are presented in Supplementary Figs 2 and 3.

Discussion

This study explored the anatomical correlates and the profile of episodic ABM impairments in patients with early-stage dementia with Lewy bodies. The main aim was to determine whether the insula, as a core region of the self,[15] is involved in the self extended in time in dementia with Lewy body patients. In summary, in the behavioural study, our findings confirm that ABM is impaired in patients with early-stage dementia with Lewy bodies, in an ungraded manner impacting all time periods, partially linked to strategic retrieval deficits, but not exclusively. Neuroimaging analyses confirm that the insular cortex is associated with ABM, namely in the self extended in time, aside from its well-known role in the present self. Additionally, we found that another crucial region of the self, the precuneus, is also associated with ABM. Other well-known regions of ABM retrieval networks, such as the parahippocampal gyri and the parietotemporal junction, were also correlated with ABM richness. Finally, the cerebellum and the putamen were correlated with ABM free recall, whereas the temporal lobe was only correlated with ABM probed recall. These results bring new insights into the role of the insular cortex in ABM, into the reliance of ABM on more elementary aspects of the self and into the behavioural characteristics of dementia with Lewy body patients.

Empirical evidence suggests that ABM impairments are a hallmark feature of dementia, such as in Alzheimer's disease, as well as in other dementia syndromes such as semantic dementia and frontotemporal lobar degeneration.[33,44] However, our study is the first to demonstrate that ABM is impaired in dementia with Lewy bodies. The present findings show an improvement in the episodic richness of memories through the provision of structured probing, notably for the dementia with Lewy body patients who displayed higher evolution rate of episodic richness, which grew by 75% in the probed recall versus the free recall, while the controls grew by 46%. These

results reinforce the idea that ABM impairments could partially pertain to a failure of the strategic retrieval process, due to the executive dysfunction characterizing dementia with Lewy bodies.[2] However, despite the provision of structured probing, patients continued to display reduced episodic re-experiencing when compared to control subjects, suggesting inability to access previously stored memories entirely. Importantly, we found that ABM impairments were temporally ungraded in dementia with Lewy body patients, with a flat performance of episodic re-experiencing across life epochs, including performance for the recent period contrary to what has been documented in Alzheimer's disease or in semantic dementia. Indeed, the neuroanatomical signature of Alzheimer's disease affects the encoding of new information and the storage of the episodic memory trace, which affects the recent period to a greater extent,[36,37] whereas recent episodic memories are relatively spared in semantic dementia.[40]

In dementia with Lewy bodies, this finding of a flat retrieval profile without greater impairment for the recent period could be related to a breakdown in research strategies,[33] whose probing would allow access to stored memories up to a limit. This flat profile could also be partially explained by a storage deficit; however, we would expect to find greater impairment for the recent period if such a deficit were to be at the forefront. Alternatively, as ABM and the subjective experience are closely linked,[9] another hypothesis could be that the subjective sense of self might be impaired, thus leading to alteration of autonoetic consciousness and disturbing access to memories, regardless of the period,[9,70] as it has already highlighted in pathology with flat profile of ABM.[35] This postulate could be reinforced by the correlation between ABM and insular atrophy that is the central finding to emerge from our study.

Indeed, concordant with our hypothesis, imaging analyses confirmed that the insular cortex, and more precisely its right posterior part, is specifically associated with ABM, whereas it was not involved in anterograde verbal memory on the RL/RI-16, which performance reflects general memory processes. The insular cortex is commonly reported to be associated with interoceptive awareness[71] and socio-emotional processes,[21] but also with social recognition memory,[72] taste memory[73] and recognition memory formation and consolidation.[74-76] Regarding dementia with Lewy bodies, our study is the first to suggest an impoverished ABM in relation to the insular atrophy occurring early in the course of the disease,[16-19] whereas the insula has been mentioned in only a few studies on ABM and is often considered as a region of secondary importance. Yet, the role of the insula is already well known in both the subjective and objective components of the present self.[5,7,20-22,77-79] As mentioned above, the subjective sense of self can readily be assessed by measuring interoceptive awareness, sense of body ownership and sense of agency and metacognition. Yet, numerous studies found that these different levels of the subjective sense of self are indeed associated with the right insula.[80-83] Specifically, the most elementary aspects of the subjective sense of self, namely interoception, sense of agency and sense of body ownership, involve the posterior insular cortex.[71,84-88] The self-concept, however, encompasses a body of autobiographical knowledge, self-esteem and self-image and has also been related to the insula in several studies.[22,83,89] Our team recently highlighted a correlation between poorer knowledge about oneself and diminished GM volume in the right insula in dementia with Lewy bodies.[6] The subjective sense of self and the self-concept are respectively elementary preconditions for episodic and semantic ABM,[10] which in turn is central for the formation and maintenance of identity in the present moment and a continuous mental representation of the self over time.[8-10,24,27,90,91] Thus, our findings suggest that the insula is a key region of the network of the self extended in time, its atrophy leading to an ABM deficit, likely through an alteration of the self at the present moment. Moreover, the fact that the posterior part of the insular cortex is involved suggests that the most elementary aspects of the self could be involved in ABM.[71,84-88] This in in line with our hypothesis whereby alteration of the most elementary component of the self, namely the subjective sense of self, would lead to impairments of higher order self-components such as ABM. However, the insula is not commonly found as a core region in other studies on ABM. An explanation could be that ABM studies in healthy subjects show a prominent involvement of brain regions involved in more elaborated aspects of the self, as in the case of the cortical midline structures, in addition to regions involved in episodic recollection. In dementia with Lewy bodies, we can speculate that it is the insular damage that prevents the grounding of the networks of the self, such as the ABM network, and leads to a global collapse of the self. Conversely, when the insula and the subjective sense of self are preserved, we can surmise that their activation is in the background, compared to activation in regions involved in episodic recollection and in more elaborated aspects of the self.

Our second main finding concerns the relationship between the right precuneus and autobiographical memories. The precuneus is considered part of the cortical midline structures,[92] which are a complex of brain regions involved in the self networks. Thus, it is already known to be a crucial component of the self, notably for processing of bodily self, namely the subjective sense of self,[93-95] but also in self-referential processing, namely the self-concept.[83,93,96-99] Beyond its role in the present self, the precuneus has also been reported to have a role in ABM, though not as a core region.[28] Interestingly, some researchers found that the precuneus was specifically involved in the retrieving of specific autobiographical events, as opposed to general past memories[100] and personal semantic information,[101] which is consistent with the notion of the precuneus being more likely related to the self and personal aspects, rather than directly to the memory aspects. Moreover, the precuneus is involved in visuo-spatial processes[102] and visual imagery processes occurring in conscious memory recall.[103,104] Our results in dementia with Lewy body patients are in line with a study on patients with posterior cortical atrophy[45] who displayed a disruption of visual and perceptual processing, as reported in dementia with Lewy body patients.[2] Ahmed *et al*. found a specific correlation between perceptual details in ABM and GM density in the precuneus; thus, impairments in perception processing and the

deprivation of visual imagery could impact recollection in ABM, acting like a barrier to mental travel in memories. Furthermore, another finding of our study, which has extensively been explored and associated with specific autobiographical memories, is the temporoparietal junction,[28] which is also known to be specifically involved in retrieval of the spatial context of events.[105]

In line with previous studies exploring ABM, we found an involvement of the medial temporal lobe, which is part of the 'core network' of ABM[28] and has already been described in healthy subjects[25,106] and in Alzheimer's disease.[37,107] Indeed, aside from its well-known role in the formation and consolidation of newly learned material,[106,108,109] the hippocampus plays a central role in autobiographical recollection, serving as an index pointing to details of the memories stored in parts of the neocortex.[28] Nevertheless, our study found no involvement of the hippocampus, but rather an involvement of bilateral parahippocampal structures, with clusters also encompassing areas of the perirhinal and entorhinal cortices, namely Brodmann area (BA) 35/36 and BA 28. This is likely due to the fact that dementia with Lewy bodies would relatively spare CA1, the larger subregion of the hippocampus, whereas neuropathological lesions are rather found in the more restricted CA2 subfield and the entorhinal cortex.[110] Yet, it is through the parahippocampal region (i.e. the perirhinal, parahippocampal and entorhinal cortices) that the hippocampus receives inputs and sends output to neocortical area.[111,112] Moreover, a large body of literature has explained the parahippocampus activity as dedicated to associative memory, that is the memory that links different items together (e.g. objects, relations, places and sounds) to make it a single composite construction, namely an episodic memory.[113-116] Thus, a parahippocampal lesion would prevent binding of the details that constitute a specific memory and thus lead to a deficit in the episodic component of ABM.

Besides the medial temporal lobe, we found, in line with other studies,[117-119] that autobiographical memories involve the lateral temporal cortex and, particularly, the left inferior temporal gyrus (BA 20). The implication of the lateral temporal lobe would be associated with autobiographical knowledge and personal semantic memory, which feed substantially autobiographical recollection.[28] Indeed, as proposed by Svoboda, most episodic memories contain semantic representations of what composes our environment, such as relatives, personal objects or even home. Moreover, life periods and life chapters constitute a frame for memories and provide a gateway to access more specific events.[8] This finding in our study is particularly relevant, since the inferior temporal gyrus was correlated only in the probed recall condition, suggesting a role in the storage of information independent of retrieval abilities, as if a semanticized version of the memory was stored in these regions. The concomitant involvement of the medial temporal lobe and the lateral temporal cortex could be accounted for by the 'transformation' theory,[120] which predicts that strictly episodic memories remain dependent on the medial temporal lobe and that a schematic version with fewer contextual details would develop in the neocortex as time goes by.

Among the other regions described in ABM imaging studies, we found a role for the right cerebellum, as highlighted in numerous studies that report medial and right lateralized involvement as a core neural signature of ABM, notably for its role in conscious retrieval of episodic memories by means of its connections to the dorsolateral prefrontal cortex.[101,121,122] These results are more convincing as the cerebellum appeared to be correlated only with the free recall condition in our study, rather suggesting an involvement as an executive process. This is concordant with the existence of a strategic retrieval deficit in dementia with Lewy body patients, as attested by a higher improvement of ABM scores after probing, compared to the controls. Interestingly, we also found a correlation between the free recall condition and the putamen, which belongs to the striatum and is part of the reward circuit and has been associated with learning and episodic memory.[123,124] Finally, our study did not reveal any correlation with the prefrontal cortex, while we might have expected it to play a role in accord with the hypothesis of an impairment in strategic retrieval. Nevertheless, we found a role for subcortical regions such as the cerebellum and the putamen, as if these regions rather than the prefrontal cortex were responsible for the executive impairments in the early stages of dementia with Lewy bodies, as is the case for attention.[125]

Overall, our study has some limitations. In particular, the sample sizes were relatively small ($n = 20$ in each group) and the results for the VBM analyses were uncorrected. Consequently, further studies involving a larger cohort of dementia with Lewy body patients will be needed to confirm our findings. Therefore, our future work aims to investigate the relationship between the subjective sense of self, the self-concept and ABM in dementia with Lewy bodies, with a special focus on the insula's role within the different components. Moreover, we will plan to analyse the self networks with a functional neuroimaging approach.

Conclusion

While evidence suggests that ABM impairments are a transdiagnostic feature of dementia, this study is the first to document them in dementia with Lewy bodies, from the early stage of the disease. We found that ABM impairments are temporally ungraded in dementia with Lewy body patients and are partially related to deficits in strategic retrieval processes, similar to what is described in frontotemporal lobar degeneration. The flat performance of episodic re-experiencing across life epochs, including the recent period, is also concordant with a global alteration of the self. The volumetric study suggests the involvement of posterior insular atrophy to account for the ABM deficit, as well as the involvement of the precuneus, two regions linked to elementary aspects of the self. This finding reinforces our hypothesis whereby insular damage would lead to a global collapse of the self, with consequences for autobiographical memories. Additionally, this study appears to be reliable since our results also revealed regions known to be part of the ABM network, such as the medial temporal lobe, which

would bind the details of the memory, the lateral temporal lobe involved in the semantic component, the temporoparietal junction associated with the spatial context and the cerebellum, a subcortical component of strategic retrieval. Finally, the different regions identified in our study draw an ABM pattern in which the insula fits nicely, as the grounding element of the phenomenological experience.

Supplementary material

Supplementary material is available at *Brain Communications* online.

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Competing interests

The authors report no competing interests.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Supplementary table 1

Mean scores on neuropsychological tests in patients with dementia with Lewy bodies

Neuropsychological evaluation	**RL/RI16**						**FAB**	**Semantic fluency**	**Phonological fluency**	**TMTA**		**TMTB**		**Digit Span**	**ROCF**
	RL1	*RT1*	*RL2*	*RT2*	*RL3*	*RT3*				*time*	*errors*	*time*	*errors*		
Patients mean score (SD)	5.1* (2.53)	11.4* (3.82)	5.75* (3.49)	12.2* (3.9)	6.05* (3.32)	12.7* (4.33)	14.11* (2.88)	20.50 (6.44)	17.25 (7.47)	72.68 (38.15	0.26* (0.56)	140.78 (68.71)	0.78 (1.05)	10.1 (2.99)	28.15* (9.09)
Normative data mean score (SD)	8.4 (2.5)	14.3 (2.1)	9.2 (2.4)	14.8 (1.8)	11.2 (2.8)	15.6 (0.8)	17.3 (0.8)	26.8 (7.4)	19.7 (6.7)	60,08 (26,76)	0 (0)	118.50 (50.67)	1 (1.35)	9 (cutoff)	31.38 (4)

FAB Frontal Assessment Battery**; RL/RI16** Rappel libre/Rappel indicé à 16 items**; ROCF** Rey-Osterrieth Complex Figure; **TMT** Trail Making Test. Data were available for 20 patients for the RL/RI16, semantic and phonological fluencies and digit span, for 19 patients for the BREF, TMTA and ROCF, and for 14 patients for the TMTB.

Scores marked with a star represent impaired scores, according to normative data.

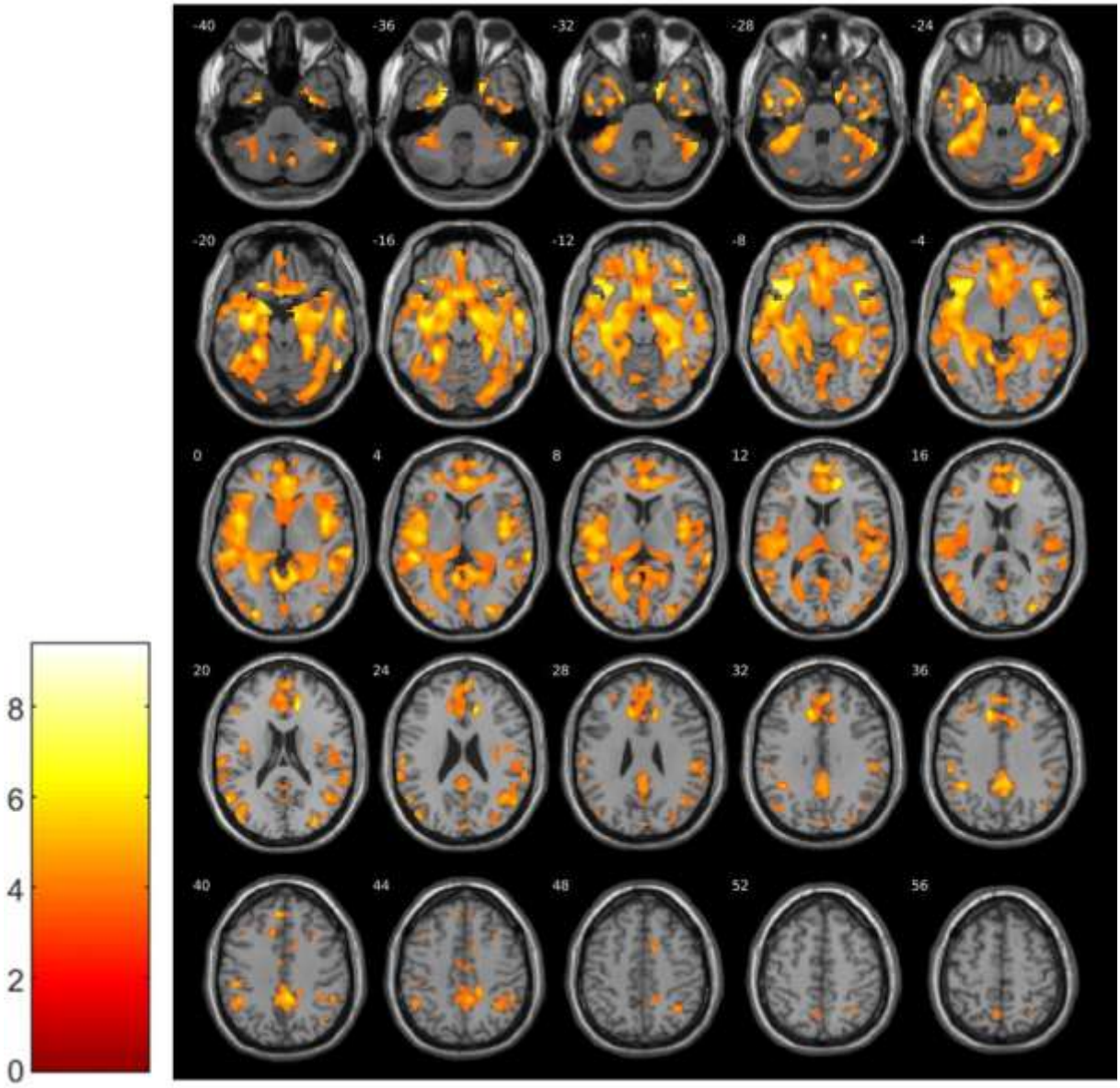
Supplementary table 2

VBM results for the free recall and probed recall conditions on the Autobiographical Interview in the dementia with Lewy bodies group

Cluster	VBM	Side	BA	*k*		*X*	*y*	*z*	T
				FRS	***PRS***				
1.	Posterior insular cortex	R	13	216/813	226/765	46.5	-27	18	3.82
	Temporoparietal junction	R	41	361/813	305/765	48	-30	21	3.74
2.	Precuneus	R	7	97/112	184/194	19.5	-72	43.5	4.48
3.	Parahippocampal gyrus	R	28/36	120/126	509/544	19.5	-3	-31.5	3.55
4.	Parahippocampal gyrus	L	35/36	393/701	423/709	-24	-21	-28.5	3.95
	Cerebellum	L	NA	109/701	104/709	-31.5	-39	-25.5	3.28
5.	Cerebellum	R	NA	93/100	-	36	-43.5	-25.5	3.43
6.	Putamen	R	NA	92/195	-	30	-7.5	-6	3.40
7.	Inferior temporal gyrus	L	20	-	77/137	-52.5	-22.5	-31.5	3.43

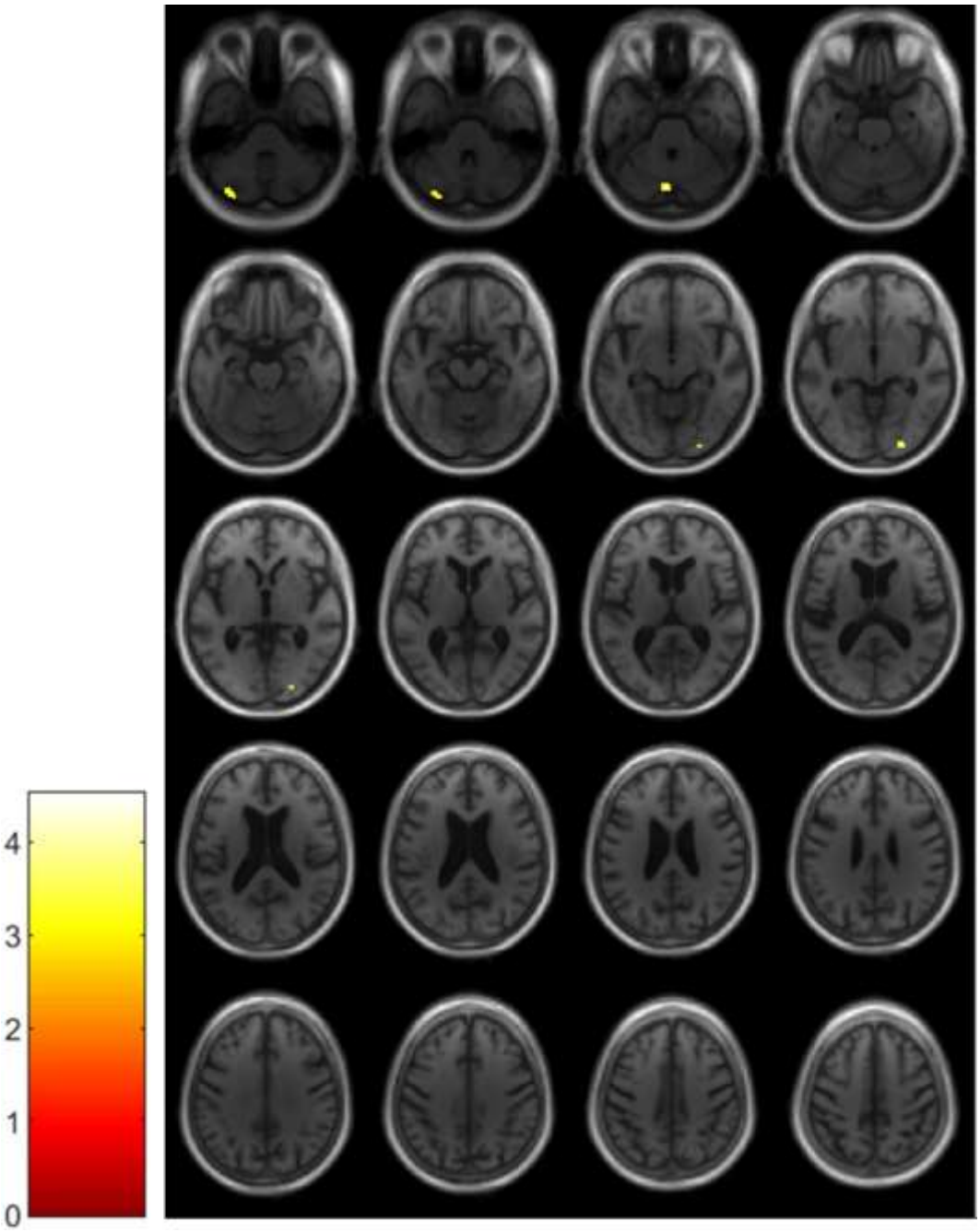
FRS free recall score, *PRS* probed recall score, *L* left, *R* right, *BA* Brodmann area, *k* cluster size in voxels (specific region's volume/cluster's global volume), x, y, z Talairach coordinates, T T-value

Supplementary figure 1



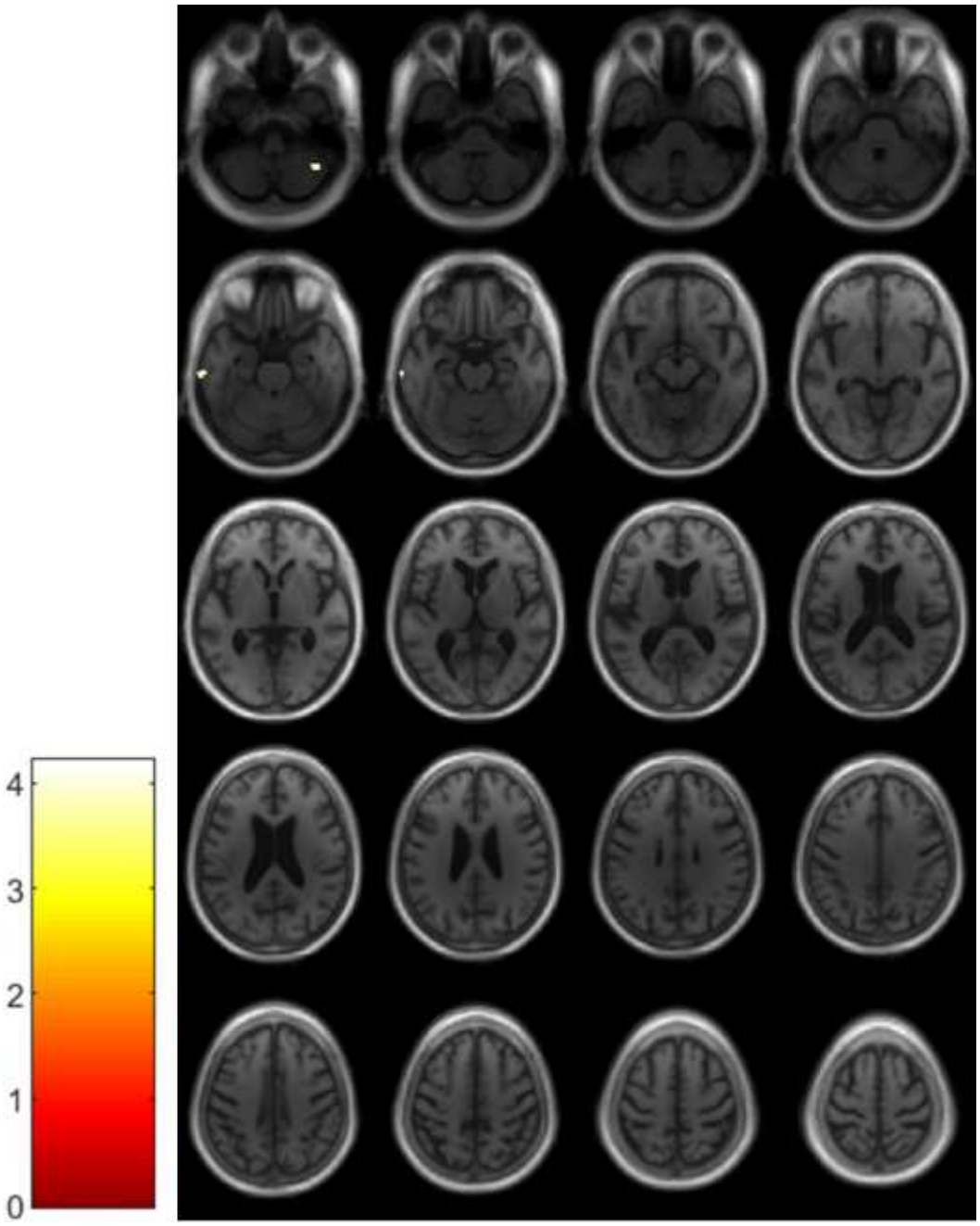
VBM analyses in LB patients compared to healthy controls. Two sample *t* test was used to compare grey matter volume in DLB patients (*n* = 20) versus control subjects (*n* = 20). Cortical thinning involving insular, temporal, occipital, frontal, cingular cortices and to a lesser extent parietal cortex in LB patients compared to healthy controls, including TIV and age as nuisance covariates ($p < .05$, FDR corrected)

Supplementary figure 2



VBM analyses for RL/RI16 1-3 free recall condition in the dementia with Lewy bodies group. Multiple linear regression was used to obtain correlation for RL/RI-16 1-3 free recall score and grey matter volume in DLB patients (*n* = 20). Grey matter volume within cerebellum is positively correlated with the 1-3 free recall score on the RL/RI16, using a threshold of *P* = .005 uncorrected, including age, gender, TIV and MMSE score as nuisance covariates, *k* = 50.

Supplementary figure 3



VBM analyses for RL/RI16 1-3 total recall condition in the dementia with Lewy bodies group. Multiple linear regression was used to obtain correlation for RL/RI-16 1-3 total recall score and grey matter volume in DLB patients (*n* = 20). Grey matter volumes within cerebellum and left lateral temporal lobe are positively correlated with the 1-3 total recall score on the RL/RI16, using a threshold of *P* = .005 uncorrected, including age, gender, TIV and MMSE score as nuisance covariates, *k* = 50.

CONCLUSION ÉTUDE 3 : Cette étude confirme qu'il existe une altération de la mémoire autobiographique dans la MCL, de manière non graduée dans le temps, impactant toutes les périodes de vie de façon homogène. L'atteinte de la mémoire autobiographique est partiellement liée à un déficit de stratégies de recherche, mais pas exclusivement, puisqu'un déficit persiste dans la condition d'indiçage spécifique.

Conformément à nos hypothèses, les analyses de neuroimagerie montrent une implication de l'insula dans les réseaux de la mémoire autobiographique, qui, par son rôle central dans le sens subjectif de soi, incarnerait une composante phénoménologique de la mémoire autobiographique, permettant l'émergence de la conscience autonoétique et du sentiment d'appartenance à soi, en particulier. Quant aux régions temporales latérales, leur présence nous conduit à suggérer qu'il pourrait exister des schémas sémantisés des souvenirs personnels dans les régions temporales latérales, servant ainsi de structure aux souvenirs. À côté des régions associées au sens subjectif de soi (i.e., cortex insulaire) et aux aspects conceptuels/sémantisés du self (i.e., cortex temporal latéral), vient s'ajouter le précuneus, qui est plus volontiers lié aux aspects de référence à soi et d'imagerie visuelle des souvenirs, qu'à ceux de la mémoire (Addis et al., 2004). Étaient également impliquées des régions du réseau central de la mémoire autobiographique, telles que les régions temporales internes qui permettraient de relier les différentes pièces du souvenir (Davachi et al., 2003; Eacott & Gaffan, 2005; Kirwan & Stark, 2004; J. Yang et al., 2008), la jonction temporo-pariétale qui est connue pour être spécifiquement impliquée dans la récupération du contexte spatial des évènements (Burgess et al., 2001, 2002). Nos analyses révélaient également un rôle pour des régions sous-corticales, telles que le cervelet et le putamen, qui seraient plutôt impliqués dans les aspects exécutifs permettant la récupération consciente des souvenirs.

Cette atteinte linéaire de la mémoire autobiographique sur les cinq périodes de vie évaluées, et corrélée à l'atrophie insulaire, est concordante avec l'hypothèse d'une atteinte globale du self. Nous suggérons que c'est l'altération du sens subjectif de soi en lien avec l'atteinte insulaire dans la MCL, qui entraine une altération de la conscience autonoétique associée au voyage mental dans le temps. Ces résultats sur l'altération de la mémoire autobiographique, à côté de ceux obtenus sur l'intéroception et le self-conceptuel, viennent conforter l'hypothèse d'un effondrement global du self dans la MCL en lien avec l'atrophie insulaire. Bien que certaines composantes du self manquent aux évaluations présentées (i.e.,

composante réflexive du sens subjectif de soi et composante sémantisée étendue dans le temps), nous nous proposons de compléter ces différentes études par une étude plus globale testant l'existence d'éventuelles corrélations entre les données comportementales obtenues dans les différents domaines déjà explorés.

5. Lien entre les composantes du self

À travers nos différentes études, nous avons montré qu'il existait une altération du sens subjectif de soi, du self-conceptuel et de la mémoire autobiographique dans la MCL. Dans cette section, nous proposons de compléter les précédentes études par une analyse globale du self, afin d'objectiver, sur la base du comportement, le lien entre le sens subjectif de soi, le self-conceptuel et la mémoire autobiographique. Le sens subjectif de soi, en tant que sujet de l'expérience, permet d'encoder les souvenirs et de voyager mentalement dans le temps pour récupérer l'information en mémoire autobiographique. De plus, le sens subjectif de soi, dans sa dimension réflexive, implique la construction des représentations mentales du self, qui forment le self-conceptuel. Le self-conceptuel entretient également des liens étroits avec la mémoire autobiographique, qui contribue elle, à la formation et assure la continuité du self-conceptuel, à travers le temps. Dans la mesure où le sens subjectif de soi, le self-conceptuel et la mémoire autobiographique semblent fortement intriqués sur le plan théorique, bien que la perception des battements cardiaques semble de prime abord éloignée des souvenirs personnels, nous faisons l'hypothèse qu'il existe un lien de corrélation entre ces trois composantes.

Nous avons mené des analyses de corrélations au moyen d'un test de Spearman entre les scores des différentes composantes du self, que nous avons présentés dans nos précédentes études. Puisque l'on peut considérer qu'il existe un continuum entre le vieillissement normal et la MCL, et que les patients de notre cohorte étaient à des stades prodromaux et très légers, les corrélations ont été testées en regroupant tous les sujets (i.e. patients atteints de MCL et sujets témoins), entre le score d'intéroception à la HTT et le nombre d'affirmations au TST, entre le score d'intéroception à la HTT et le score total à l'AI, et entre le nombre d'affirmations au TST et le score total à l'AI.

Les résultats sont présentés dans la figure 8, et montrent des corrélations positives significatives entre les scores aux TST et la HTT ($r = 0.46$, $P = 0.003$), aux TST et à l'AI ($r = 0.76$, $P < 0.001$), et à la HTT et à l'AI ($r = 0.49$, $P = 0.001$), respectivement.

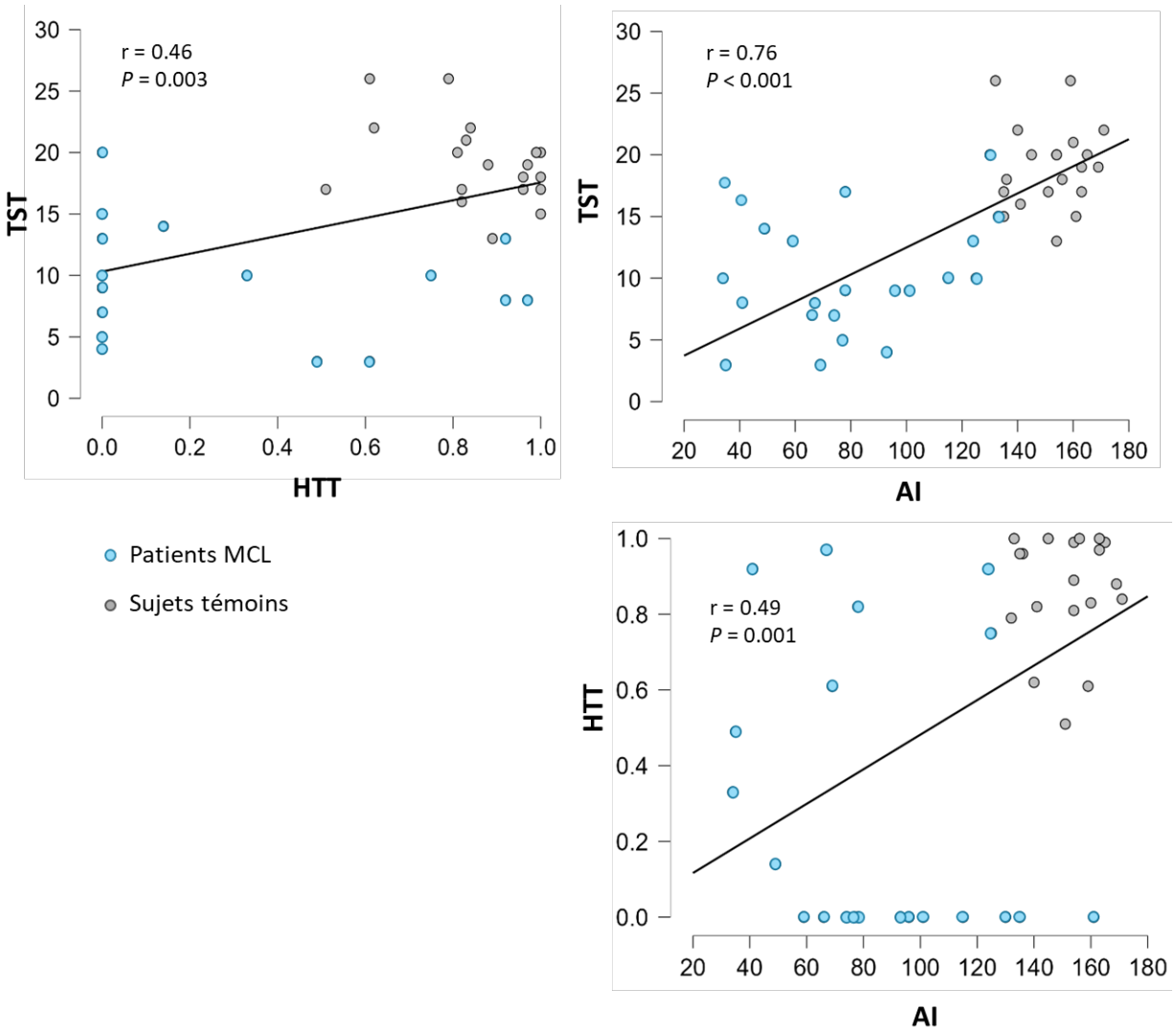


Figure 8 *Analyses de corrélations entre les différentes composantes du self chez les patients atteints de maladie à corps de Lewy et les sujets témoins. HTT Heartbeat tracking task, AI Autobiographical Interview, TST Twenty Statements Test*

L'analyse globale des trois études comportementales confirme donc l'existence de corrélations entre les différentes composantes du self : l'altération de la détection des battements cardiaques reflétant le sens subjectif de soi, l'appauvrissement des affirmations sur soi pour le self-conceptuel, et l'appauvrissement des souvenirs personnels pour la mémoire autobiographique. De plus les résultats des trois études d'imagerie font ressortir l'insula comme région commune à ces composantes du self. Ces résultats, qui confortent l'hypothèse d'une altération globale du self liée à l'atrophie insulaire dans la MCL, seront débattus dans la discussion générale de ce manuscrit.

LE SELF DANS LA MALADIE À CORPS DE LEWY : DISCUSSION & CONCLUSIONS

DISCUSSION GÉNÉRALE

Ces travaux de thèse visaient à enrichir les connaissances sur le self et à en explorer les différentes composantes dans la MCL. Nous avons prêté un intérêt particulier à l'insula, qui occupe une place centrale dans les réseaux du self (cf. Partie théorique, 2. Self & insula), en particulier dans ses aspects les plus élémentaires (Craig, 2002). À travers les différentes études que nous avons présentées dans le manuscrit de cette thèse, nous nous sommes appuyés sur le modèle du self proposé par Prebble (Prebble et al., 2013), afin d'analyser le sens subjectif de soi, le self-conceptuel et la mémoire autobiographique. Il s'agit, à notre connaissance, des premiers travaux s'intéressant à ces thématiques dans la MCL, qui constitue un modèle d'étude privilégié pour explorer le self puisqu'elle se caractérise par une diminution de volume précoce de l'insula (Blanc et al., 2015; Roquet et al., 2017). Conformément à nos hypothèses, nos travaux ont permis d'objectiver une altération des différentes composantes du self dans la MCL. Nous avons montré qu'il existait une atteinte de l'intéroception (cf. Partie expérimentale, 2. Étude du sens subjectif de soi dans la MCL), qui définit l'expérience préréflexive et fait partie du sens subjectif de soi. Nous avons également constaté un appauvrissement des représentations de soi (cf. Partie expérimentale, 3. Étude du self-conceptuel dans la MCL), qui alimentent le self-conceptuel, ainsi qu'une altération des aspects épisodiques de la mémoire autobiographique (cf. Partie expérimentale, 4. Étude de la mémoire autobiographique épisodique dans la MCL), qui fait référence au self phénoménologique étendu dans le temps. De plus, l'analyse globale des différentes composantes du self a montré que les trois composantes sont corrélées entre elles (cf. Partie expérimentale, 5. Lien entre les composantes du self). Enfin, nous avons identifié les substrats anatomiques associés aux différents aspects du self, qui convergeaient vers l'insula en tant que région commune. Du point de vue théorique, nous avons pu montrer qu'il existait un lien entre les différentes composantes du self et que l'atteinte du sens subjectif de soi semblerait être associée à un effondrement global du self. Du point de vue des neurosciences cognitives, nous avons pu analyser les corrélats anatomiques des différentes composantes du self, dont nous avons fait la synthèse dans la figure 10, illustrant la place centrale de l'insula. Enfin, du point de vue clinique, nous avons pu caractériser l'atteinte du self dans la MCL, ce qui pourrait conduire à l'élaboration de nouvelles pistes de prise en charge centrées sur le self.

À travers ce corpus d'études, nous avons mis en lumière l'existence d'une altération de l'ensemble des composantes du self dans la MCL comparativement au vieillissement normal, en partant du sens subjectif de soi préréflexif qui est le niveau le plus basique, évalué par la HTT (Schandry, 1981), à des niveaux plus élaborés tels que le self conceptuel évalué par le TST (Kuhn & McPartland, 2017) et la mémoire autobiographique évaluée par l'AI (Levine et al., 2002). Nous avons complété ces trois volets comportementaux par une étude corrélationnelle entre les différentes composantes du self (cf. Partie expérimentale, 5. Lien entre les composantes du self). Ces analyses ont été menées en regroupant les populations de patients et sujets sains, en considérant qu'il existe un continuum entre vieillissement normal et MCL, dans la mesure où les patients étaient atteints de MCL très légère à prodromale. Bien que la détection des battements cardiaques puisse sembler très éloignée des représentations de soi et des souvenirs autobiographiques, les analyses ont montré que les trois composantes sont corrélées entre elles. Ces résultats indiquent l'existence d'un lien entre le sens subjectif de soi, le self-conceptuel et la mémoire autobiographique, comme nous en avions fait l'hypothèse, et comme l'avaient élégamment proposé Prebble et collaborateurs (Prebble et al., 2013) avant nous. Si les analyses corrélationnelles ne permettent pas de déduire le sens des relations qu'entretiennent les différentes composantes, on peut supposer que le sens subjectif de soi constitue la base du self du fait de son caractère élémentaire. Ainsi, son altération pourrait impacter les composantes plus élaborées telles que le self-conceptuel et la mémoire autobiographique ; en d'autres termes, l'atteinte du sens subjectif de soi semblerait être à l'origine d'un effondrement global du self. Ce postulat va dans le sens de ce qui a déjà été proposé dans les travaux de Philippi (cf. Figure 9; Philippi, 2017), qui s'appuyaient également sur le modèle de Prebble (Prebble et al., 2013). Ces travaux, menés sur une population de patients atteints de MA, soulignaient que l'anosognosie était corrélée à l'appauvrissement des affirmations sur soi et des souvenirs personnels. La conscience des troubles fait partie d'un niveau réflexif du sens subjectif de soi que Prebble et collaborateurs nomment « *self-awareness* », et qui servirait de prérequis aux autres composantes du self. Nos travaux viennent compléter ces résultats en s'appuyant sur la MCL, qui constitue plus volontiers que la MA, un modèle d'étude privilégié du sens subjectif de soi à un niveau plus élémentaire, préréflexif. Notre population de patients se caractérisait en effet par un déficit intéroceptif marqué avec plus de 60% des patients qui ne parvenaient pas à détecter leurs battements.

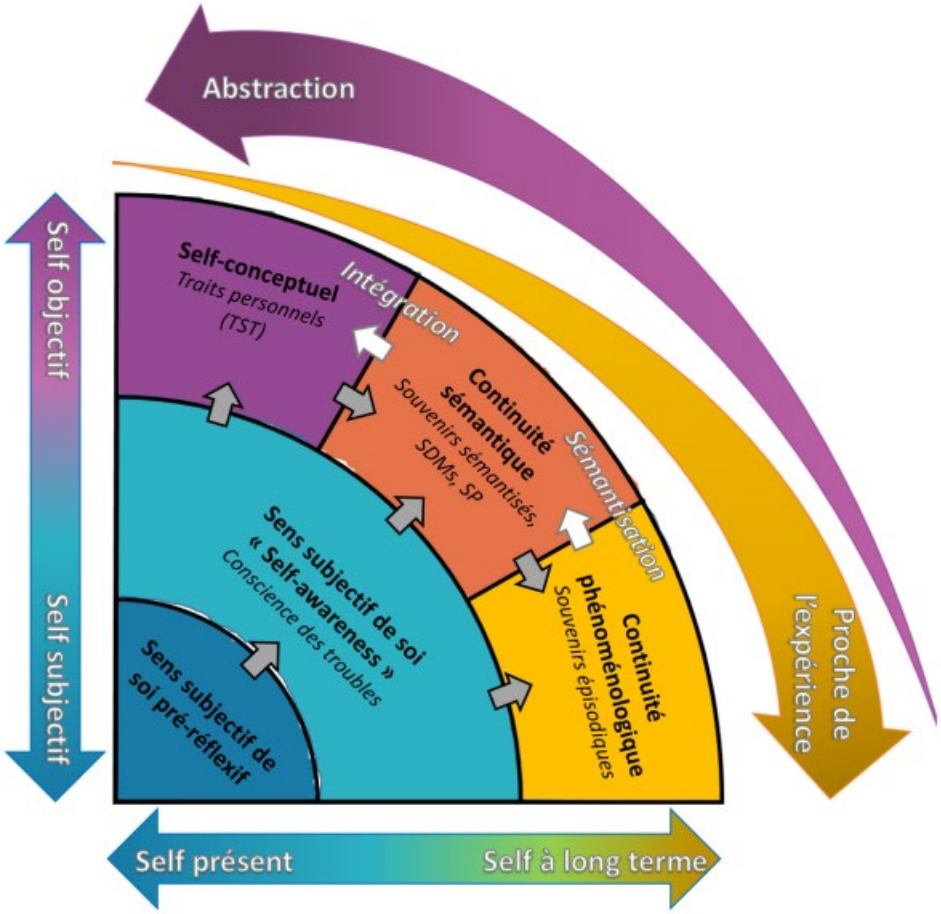


Figure 9 *Schéma récapitulatif du self représentant ses différentes composantes selon leurs caractéristiques principales (Philippi, 2017)*

cardiaques (cf. Partie expérimentale, 2. Étude du sens subjectif de soi dans la MCL). Ces résultats mériteront d'être complétés par l'étude de la conscience des troubles que l'on s'attendrait à trouver altérée chez ces patients qui paraissent fréquemment anosognosiques ou anosodiaphoriques, dès les stades précoces de la maladie (Calil et al., 2021). C'est également ce que prédit le modèle proposé par Prebble et collaborateurs, selon lequel l'atteinte du sens subjectif de soi à un niveau préreflexif devrait entrainer une atteinte du niveau réflexif, et finalement un effondrement global du self (Prebble et al., 2013). L'expérience préreflexive nous confère le sentiment que notre personne est le sujet de l'expérience vécue, qu'il s'agisse d'un phénomène interne comme les battements du cœur ou d'un phénomène externe comme la sensation de l'air frais que l'on respire. L'expérience préreflexive permet l'émergence du niveau dit « *self-awareness* » qui implique une conscience réflexive, permettant l'analyse de ses pensées, sentiments, comportements, expériences (Keenan et al., 2005; Leary & Tangney, 2012; Lewis, 1991; Schooler, 2002; Stuss

& Levine, 2002). Finalement, le sens subjectif de soi serait, d'une part indispensable pour encoder l'expérience vécue (Klein et al., 2004; Moscovitch, 1995; Prebble et al., 2013), mais également directement associé à la conscience autonoétique, qui permet de rappeler les souvenirs personnels.

Concernant le lien entre le sens subjectif de soi et la mémoire autobiographique, peu d'études expérimentales ont analysé le lien entre les deux composantes. Notre étude sur la mémoire autobiographique en elle-même suggère que l'altération des souvenirs personnels serait secondaire à une atteinte du self (cf. Partie expérimentale, 4. Étude de la mémoire autobiographique dans la MCL). En effet, l'étude a démontré l'existence d'une atteinte épisodique non graduée dans le temps, nous conduisant à incriminer le sens subjectif de soi ou des processus exécutifs, plutôt que les capacités mnésiques, dont l'atteinte aurait volontiers été caractérisée par une altération plus franche des souvenirs récents (Eustache et al., 2004; Graham & Hodges, 1997; Irish et al., 2011; Kopelman et al., 1989). Notre hypothèse est, d'une part, confortée par l'étude d'imagerie volumétrique des patients MCL, à travers l'implication de l'insula, qui est plus vraisemblablement liée aux aspects élémentaires du self, qu'à des processus exécutifs, et d'autre part, par la mise en évidence de corrélations entre les performances en mémoire autobiographique et la détection des battements cardiaques, sur l'ensemble des participants. Outre la perte présumée de la référence à soi liée à l'atteinte du sens subjectif de soi, l'altération des capacités à détecter les battements cardiaques pourrait plus particulièrement réduire la sensation de reviviscence de la composante émotionnelle des souvenirs épisodiques, comme c'est le cas pour le ressenti des émotions, de façon plus générale (Damasio, 2003). À l'image de nos résultats, quelques études récentes ont souligné l'existence d'un lien robuste entre le sens subjectif de soi et la mémoire autobiographique, en particulier à travers des expériences de réalité virtuelle manipulant la perspective du sujet de l'expérience. Il a par exemple été montré, dans des populations saines, que la récupération des détails épisodiques était meilleure lorsqu'une scène était vécue et encodée dans la perspective d'acteur (i.e., première personne) que dans la perspective de spectateur (i.e., troisième personne, ou lorsque sa propre personne physique apparait dans la scène) (Bergouignan et al., 2014, 2022; Bréchet et al., 2019). De plus, l'encodage dans la perspective d'acteur impliquerait davantage les réseaux cérébraux de la mémoire autobiographique que dans la perspective spectateur (Iriye & St. Jacques, 2020). Par ailleurs, une étude chez des

patients atteints de schizophrénie suggérait que l'association entre la schizophrénie et une mémoire autobiographique appauvrie (Berna et al., 2015) était médiée par un déficit de métacognition (Mediavilla et al., 2021), qui relève de la composante « *self-awareness* », du sens subjectif de soi. Il sera intéressant de tester dans notre population un éventuel lien entre la mémoire autobiographique et des fonctions relevant du niveau réflexif du sens subjectif de soi, telle que l'anosognosie. Cela a été étudié dans la MA et certains auteurs ont mis en évidence un lien entre la conscience des troubles et les performances en mémoire autobiographique (Naylor & Clare, 2008 ; Philippi 2017). De manière intéressante, une étude dans la MA a également montré que l'anosognosie pour la mémoire était associée à une dysconnexion entre des régions associées au self, telles que la ligne corticale médiane et des régions impliquées dans la mémoire autobiographique, telles que les régions temporales médianes (Perrotin et al., 2015). L'ensemble de ces travaux soutient l'idée qu'à travers ses deux composantes (i.e. expérience préréflexive et « *self-awareness* »), le sens subjectif de soi semble jouer un rôle essentiel dans la construction et la restitution du self autobiographique. Parallèlement à son implication dans les aspects phénoménologiques du self, le sens subjectif de soi serait également lié au self-conceptuel. Nous avons montré dans notre étude que le self conceptuel, évalué par la capacité à fournir des affirmations sur soi, apparait effrité dans la MCL (cf. Partie expérimentale, 3. Étude du self-conceptuel dans la MCL), reflétant un appauvrissement des représentations de soi. L'hypothèse selon laquelle cette composante serait altérée secondairement à l'atteinte du sens subjectif de soi est confortée par la mise en évidence de corrélations avec la capacité à détecter les battements cardiaques, d'une part, et l'atrophie insulaire, d'autre part. Peu d'études se sont intéressées au lien entre sens subjectif de soi et self-conceptuel. Néanmoins, une étude sur la reconnaissance faciale a montré qu'il existait un biais de reconnaissance de son propre visage, dont les caractéristiques visuelles sont pourtant stockées et sont inhérentes au self-conceptuel, lorsque des stimuli tactiles étaient synchrones avec la vision du visage d'un autre individu. Les auteurs ont suggéré que l'intégration multisensorielle pouvait modifier les représentations internes de soi (Tsakiris, 2008). Une étude de réalité virtuelle a fait le lien entre le sens subjectif de soi et le self conceptuel, ainsi que la mémoire autobiographique (Tacikowski et al., 2020). Il s'agissait d'une expérience dans laquelle les sujets avaient l'illusion d'être dans le corps d'un proche, et à l'issue de laquelle ils devaient remplir un questionnaire de personnalité, suivi d'une tâche de

reconnaissance en mémoire. Les auteurs ont montré que l'illusion d'être dans le corps d'un proche modifiait les croyances des participants concernant leur propre personnalité, qu'ils avaient tendance à faire converger vers la personnalité de leur proche. De plus, l'intégration de la personnalité du proche était associée à une meilleure reconnaissance des événements vécus dans le corps de leur proche, que dans les cas où il y avait des incongruences avec la personnalité du proche. Ainsi, ces résultats suggèrent qu'une dissociation entre le sens subjectif de soi et le self-conceptuel pourrait être à l'origine d'un sentiment d'incohérence, perturbant ainsi l'encodage des informations, et par conséquent, le vécu de l'expérience.

Le lien entre la mémoire autobiographique et le self-conceptuel peut sembler plus évident, et a de ce fait été davantage étudié. La perspective qu'une relation réciproque existe entre les deux composantes est partagée par de nombreux auteurs : les représentations de soi imprègnent les souvenirs autobiographiques, qui eux même contribuent à la formation du self-conceptuel (Prebble et al., 2013). Nos résultats de l'analyse globale du self menée sur l'ensemble des participants confirment un lien entre l'appauvrissement de notre « banque de représentations sur soi » évaluée à l'aide du TST et nos capacités à rappeler des souvenirs personnels avec l'AI. Cela est concordant avec ce qui a été montré dans la MA par Philippi (2017). L'étude d'Addis & Tippett dans la MA a, quant à elle, mis en évidence qu'il existait une diminution des représentations sur soi, en lien avec la perte des souvenirs de la période d'enfance uniquement (Addis & Tippett, 2004). Comme cela l'a été suggéré par des experts tels que Conway ou Rathbone (Conway, 2005; Conway et al., 2004; Conway & Pleydell-Pearce, 2000; Rathbone et al., 2008), nous construisons et façonnons notre identité en nous appuyant sur des événements du passé, en particulier les souvenirs de la période adulte jeune qui voit émerger le self-conceptuel stable et durable, et qui correspond au pic de réminiscence. Dans une étude s'intéressant à la relation entre le self-conceptuel et les souvenirs personnels chez des sujets sains (Rathbone et al., 2008), il était demandé aux participants, dans un premier temps, de produire des déclarations sur eux-mêmes, reflétant leur identité, puis dans un second temps d'associer les déclarations qui leur correspondaient le mieux, à un souvenir personnel. Les auteurs ont montré que les participants étaient en mesure de fournir des souvenirs associés à des caractéristiques spécifiques du self, et que ces souvenirs étaient normalement distribués autour du pic de réminiscence, suggérant que l'activation d'une représentation de soi conduirait à l'activation d'un réseau de souvenirs d'événements associés

à cette représentation. Une autre étude a tenté de répondre à la question du lien entre le self-conceptuel et la mémoire autobiographique dans la MA (El Haj & Antoine, 2017), en invitant les participants à rappeler des souvenirs autobiographiques, soit après avoir fourni des représentations sur eux-mêmes, soit après avoir lu un texte dans la condition contrôle. L'objectif était d'analyser l'impact de la génération d'informations liées au self-conceptuel, sur le rappel en mémoire autobiographique. Les auteurs ont montré qu'il existait une meilleure spécificité des souvenirs, avec davantage de détails épisodiques et une meilleure reviviscence du souvenir, lorsque la tâche de mémoire autobiographique était précédée d'une tâche de déclarations sur soi, plutôt que d'une tâche de lecture d'un texte, comme si la génération d'informations liées au self-conceptuel stimulait la mémoire autobiographique. Si les représentations du self sont formées à partir des souvenirs autobiographiques, et qu'elles peuvent, en retour, amorcer la récupération de certains souvenirs, elles pourraient toutefois être stockées indépendamment de la mémoire autobiographique (Kihlstrom et al., 2003; Kihlstrom & Klein, 1997; Klein & Gangi, 2010; Klein & Loftus, 1993). Cette théorie est soutenue par les travaux Tulving et son célèbre patient K .C. (Tulving, 1993) ou encore par Klein et al., qui ont restitué de nombreux cas cliniques de patients cérébrolésés, atteints de troubles du spectre autistique ou encore de MA, dont la connaissance sur les traits de personnalité semble résister à l'atteinte de la mémoire autobiographique épisodique (Klein et al., 1999, 2003; Klein & Gangi, 2010). À travers son schéma inspiré du modèle de Prebble (cf. figure 9), et comme elle l'a mis en évidence dans la MA, Philippi (2017) suggère par ailleurs que le self-conceptuel serait plus particulièrement lié à la composante sémantisée de la mémoire autobiographique, grâce à des processus de sémantisation et d'intégration de souvenirs marquants (e.g., « En 2020, durant la belle saison, j'allais régulièrement faire de l'escalade sur le site de Klingenthal avec des amis. Un dimanche de septembre, j'ai fini par achever la voie « parfum exotique », qui me paraissait pourtant infranchissable en tête. J'ai compris qu'il fallait se donner les moyens, et que j'étais capable de cette détermination »), ce qui a également été proposé dans d'autres travaux (Blagov & Singer, 2004; Pasupathi et al., 2007; Rathbone et al., 2019). Nous prévoyons dans un travail à venir d'étudier le lien entre le self-conceptuel, la composante sémantisée de la mémoire autobiographique et les souvenirs définissant le soi dans la MCL, que nous supposons également altérés dans le contexte d'atteinte globale du self, qui semblerait être lié à l'altération du sens subjectif de soi.

Concernant les substrats anatomiques du self, conformément à notre hypothèse de travail, l'insula apparait comme la région commune aux différentes composantes du self explorées. Nous proposons un schéma de synthèse reprenant les résultats de neuroimagerie les plus pertinents de nos études, confrontés aux données de la littérature (cf. figure 10). Le schéma suit une organisation modulaire et hiérarchique, qui suppose que les différents modules se cumulent pour former les réseaux cérébraux associés aux différentes composantes du self, selon leur niveau de complexité. Le sens subjectif de soi préréflexif, qui est le niveau le plus élémentaire et constitue un prérequis à toutes les autres composantes, y est représenté en bleu. Dans notre étude sur l'intéroception, la confrontation des régions les plus atrophiques chez les patients les plus déficitaires, avec les données de la littérature, fait ressortir l'insula et le cortex cingulaire antérieur (cf. Partie expérimentale, 2. Étude du sens subjectif de soi dans la MCL). Le self-conceptuel, qui est plus concret et fait référence à l'objet de l'expérience

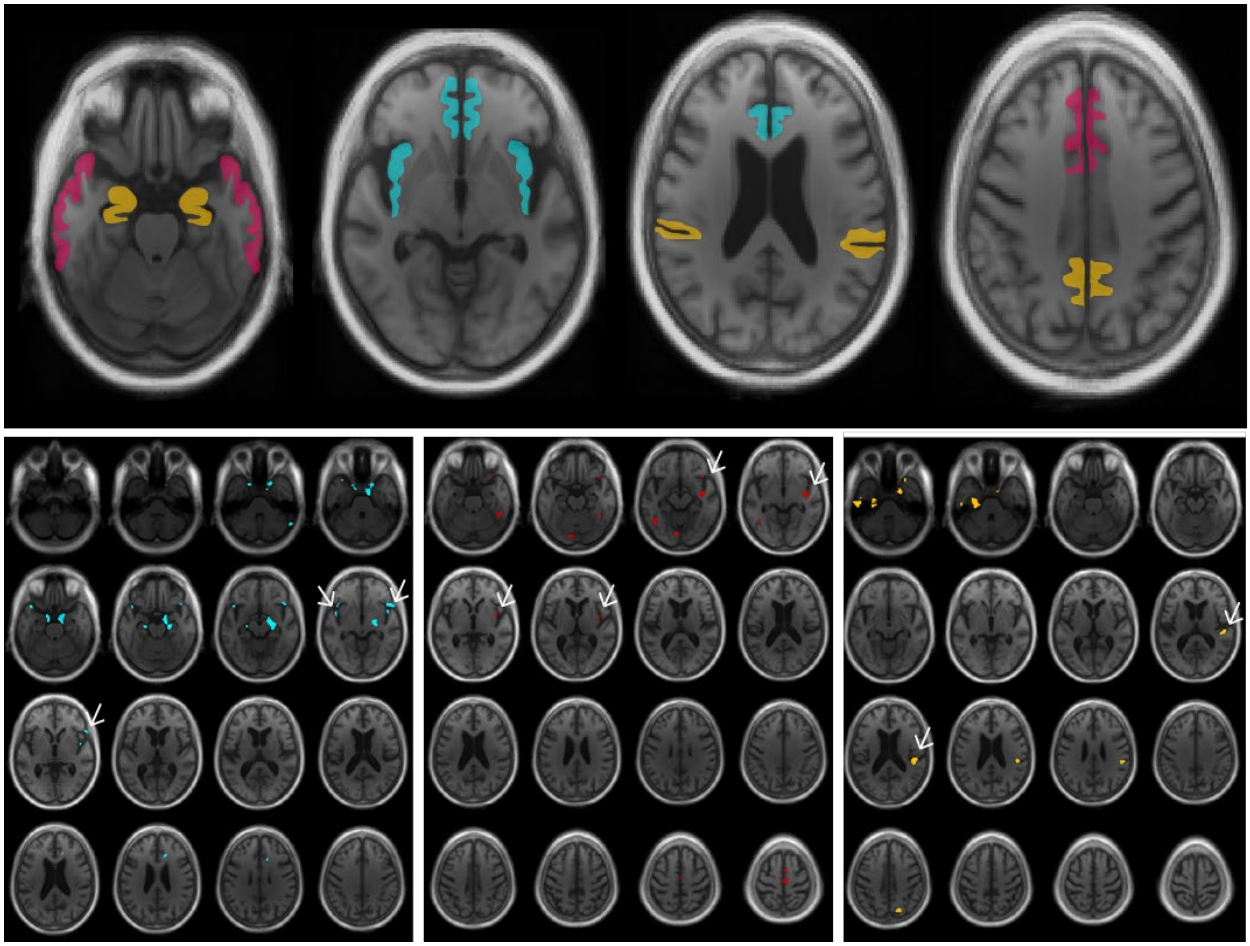


Figure 10 *Synthèse des régions anatomiques du self sur la base de ce qui a été trouvé dans nos études (voir les trois vues d'ensemble dans la partie inférieure de la figure, les flèches y indiquent l'insula), confronté à la littérature. Le sens subjectif de soi y est représenté en bleu, le self-conceptuel en rouge et la mémoire autobiographique en jaune.*

et aux représentations crées par le sens subjectif de soi, est représenté en rouge. Il implique, en plus du cortex insulaire associé au sens subjectif de soi, les régions temporales latérales et des régions de la ligne corticale médiane antérieure, telle que l'aire motrice supplémentaire (cf. Partie expérimentale, 3. Étude du self-conceptuel dans la MCL). Enfin, la mémoire autobiographique épisodique, qui renvoie à des aspects hautement sophistiqués du self, est représentée en jaune. Ses substrats anatomiques sont plus complexes puisqu'ils comprennent ceux du sens subjectif de soi et du self-conceptuel, auxquels s'ajoutent les régions temporales médianes, la jonction temporo-pariétale et les régions postérieures de la ligne corticale médiane, comme le précuneus. Comme nous en avions fait l'hypothèse, nos travaux confirment que le point commun de ces trois composantes se situe dans la région insulaire, qui semble constituer un point d'ancrage aux différents réseaux du self.

Il était déjà admis que l'insula est impliquée dans les fonctions basiques du self (Craig, 2009). En effet, à travers une revue approfondie de la littérature, Craig soutenait l'idée que l'insula serait la région cérébrale au cœur d'un large éventail de fonctions impliquant les aspects primaires de la conscience humaine, telles que l'intéroception (Craig, 2003), le sens d'« *ownership* » (Tsakiris et al., 2007) et le sens d'agentivité (Farrer et al., 2003; Farrer & Frith, 2002) ou encore la reconnaissance de soi dans le miroir (Devue et al., 2007). Nos découvertes permettent à présent de proposer que l'insula soit impliquée dans un schéma plus complexe de conscience de soi, comprenant ses aspects les plus élaborés comme le self-conceptuel et la mémoire autobiographique épisodique.

Notre étude sur le sens subjectif de soi préreflexif (cf. Partie expérimentale, 2. Étude du sens subjectif de soi dans la MCL) a permis de montrer que les patients qui échouaient l'épreuve de perception des battements cardiaques, avaient une atrophie plus marquée de l'insula, à côté du cortex cingulaire antérieur, des régions temporales médianes, de la région temporale latérale et du cervelet. Bien que nous n'ayons pas pu mener d'étude corrélationnelle, les résultats confortent l'implication de l'insula dans l'intéroception, et complètent ceux d'études précédentes dans d'autres populations de patients (Garcia-Cordero et al., 2016; Salamone et al., 2021 ; Salvato et al., 2018). La présence d'une atrophie du cortex cingulaire antérieur marquée chez ces patients n'est pas surprenante puisque c'est une région structurellement et fonctionnellement proche de l'insula antérieure, comprenant toutes deux des neurones de Von Economo (Allman et al., 2010 ou 2011 ; Fathy et al. 2020). Comme d'autres régions de la

ligne corticale médiane, le cortex cingulaire antérieur est impliqué dans différents aspects du sens subjectif de soi préréflexif, tels que la détection des battements cardiaques, l'agentivité ou encore la reconnaissance de son propre visage (Critchley et al., 2004; Frith, 2002; T. T. J. Kircher et al., 2001; Northoff et al., 2006; Northoff & Bermpohl, 2004), et du sens subjectif de soi réflexif, par exemple dans la conscience émotionnelle et l'anosognosie (Guerrier et al., 2018; Smith et al., 2019). Son activation dans ces fonctions primaires est par ailleurs souvent conjointe à celle de l'insula (Craig, 2009; Medford & Critchley, 2010).

Ainsi, l'insula apparait comme un noyau multiconnecté dont le rôle central serait de conférer le sentiment de soi, permettant de discriminer ce qui appartient au soi, de ce qui appartient au non-soi. Finalement, c'est le sens subjectif de soi, à la base de l'organisation hiérarchique du self, qui permettrait à un individu de reconnaitre un souvenir ou un attribut comme lui appartenant. Ce serait ainsi par l'association de l'insula à d'autres régions cérébrales que des aspects plus élaborés du self pourraient émerger. Nous l'avons montré pour le self-conceptuel (cf. Partie expérimentale, 3. Étude du self conceptuel dans la MCL) dont nous proposons que l'existence repose en partie sur l'insula pour les aspects de référence à soi (Eisenberger et al., 2011; Modinos et al., 2009), associée à d'autres régions cérébrales, pour les aspects conceptuels. Parmi les régions classiquement associées au self et aux processus de référence à soi, figure également la ligne corticale médiane (Northoff & Bermpohl, 2004). Ainsi, nous aurions pu attendre que le cortex cingulaire apparaisse dans notre étude sur le self-conceptuel, mais nos résultats ont plus volontiers souligné un rôle pour l'aire motrice supplémentaire. Cette aire est impliquée dans l'agentivité (David et al., 2008; Farrer et al., 2003; Farrer & Frith, 2002) et pourrait contribuer à la représentation du self corporel (Dary et al., 2023). Le rôle de l'aire motrice supplémentaire a par ailleurs déjà été souligné dans une étude sur la référence à soi, lors d'une tâche semblable au TST, i.e., de réflexion sur ses traits de personnalité et ses caractéristiques physiques (Kjaer et al., 2002). De plus, l'aire motrice supplémentaire comprend des neurones miroirs (Mukamel et al., 2010), connus pour être impliqués dans l'exécution d'un acte moteur, ou dans l'observation d'un même acte réalisé par une autre personne (Jacob & Jeannerod, 2005; Rizzolatti & Craighero, 2004), mais le système des neurones miroirs est également activé lors du sentiment d'empathie (Iacoboni, 2005), et sous-tendrait la théorie de l'esprit (Siegal & Varley, 2002). De tels mécanismes permettraient d'alimenter la conscience de soi, sur laquelle pourrait se construire la

conscience des autres, comme c'est le cas pour les régions de la ligne corticale médiane (Happé, 2003; Saxe, 2009). De manière intéressante, nous avons identifié dans notre étude les gyri fusiforme et lingual qui sont connus pour leur implication respective dans la reconnaissance des visages (Bruce & Young, 1986; Kanwisher et al., 1997; T. T. Kircher et al., 2000) et l'imagerie visuelle (Bogousslavsky et al., 1987; Y. Yang et al., 2015), ce qui laisse supposer que le self-conceptuel pourrait solliciter des processus d'imagerie mentale visuelle, afin de visualiser sa personne. Concernant les aspects associés aux concepts du self, notre étude a montré un rôle pour les régions temporales latérales antérieures, qui constituent le support classique des connaissances sémantiques en général (Levy et al., 2004; Schmolck et al., 2002). Outre le cortex insulaire et les régions temporales latérales, soulignons que l'étude du self-conceptuel n'a pas mis en évidence d'autres régions communes avec la mémoire autobiographique, ce qui conforte l'idée que le self-conceptuel repose sur des substrats anatomiques distincts, et qu'il n'est pas nécessaire de faire appel aux souvenirs autobiographiques pour accéder aux représentations de soi.

Concernant la mémoire autobiographique, conformément à nos hypothèses, notre étude a révélé une implication de l'insula (cf. Partie expérimentale, 4. Étude de la mémoire autobiographique épisodique dans la MCL), qui, par son rôle dans le sens subjectif de soi, pourrait représenter les aspects phénoménologiques de la mémoire autobiographique, permettant la conscience autonoétique. Quant aux régions temporales latérales, leur apparition dans la condition indicée nous conduit à suggérer qu'il pourrait exister des schémas sémantisés des souvenirs personnels dans les régions temporales latérales, servant ainsi de structure aux souvenirs. À côté des régions associées au sens subjectif de soi (i.e., cortex insulaire) et au self-conceptuel (i.e., cortex temporal latéral), vient s'ajouter le précuneus. C'est une région de la ligne corticale médiane, impliquée dans les réseaux du self et en particulier du sens subjectif de soi (Farrer & Frith, 2002; Lyu et al., 2023; Ruby & Decety, 2001), mais également dans les processus d'imagerie visuelle durant le rappel conscient en mémoire (Fletcher et al., 1995; Freton et al., 2014). Une autre région, associée à la mémoire autobiographique et connue pour être au cœur de ses réseaux, est la jonction temporopariétale (Svoboda et al., 2006), qui contribue à la récupération du contexte spatial des événements (Burgess et al., 2001, 2002). Nous avons également identifié les gyri parahippocampiques, qui sont étroitement liés aux hippocampes, et permettraient d'associer

les différentes pièces du souvenir, en particulier les informations sensorielles (Davachi et al., 2003; Eacott & Gaffan, 2005; Kirwan & Stark, 2004; J. Yang et al., 2008). Nous n'avons pas identifié de corrélations avec les hippocampes, dont le rôle dans la mémoire autobiographique épisodique est bien admis (Scoville & Milner, 1957; Svoboda et al., 2006). Cela pourrait être lié au fait que la MCL épargne relativement CA1 qui correspond à la sous-région la plus large de l'hippocampe, tandis que les lésions neuropathologiques sont plus volontiers identifiées dans CA2 et dans le cortex entorhinal (Adamowicz et al., 2017). Finalement, notre étude a montré l'implication du cervelet et du putamen, qui pourraient participer à la récupération stratégique des souvenirs alors que les régions préfrontales ventrolatérales classiquement décrites (Svoboda et al. 2006) n'ont pas été mises en évidence, probablement parce qu'elles ne sont pas significativement atrophiées chez les patients (cf. Figure 7 ; partie expérimentale, 1.5. Imagerie volumétrique). Nous aurions également pu nous attendre à trouver le cortex préfrontal médian et le cortex cingulaire postérieur qui sont souvent mis en évidence dans les réseaux de la mémoire autobiographique (Maguire, 2001; Svoboda et al., 2006) et qui apparaissent pourtant bien atrophiés chez nos patients. Il sera intéressant de compléter l'étude en imagerie volumétrique par une étude de la connectivité fonctionnelle. Nous pourrions supposer que l'atteinte des processus élémentaires du self, liée à l'atrophie insulaire, est prépondérante dans le déficit en mémoire autobiographique chez nos patients, effaçant alors l'implication d'autres régions. Inversement, le fait que l'insula ne ressorte pas dans les études de la mémoire autobiographique chez des sujets sains ou dans des populations de patients qui n'ont pas une atteinte insulaire significative, pourrait être expliqué par le fait que les aspects élémentaires du sens subjectif de soi liés à l'insula constituent un processus d'arrière-plan, qui n'est pas prépondérant dans l'expression de la mémoire autobiographique, lorsque ces aspects élémentaires sont préservés.

Il convient de mentionner que nos travaux présentent quelques limites, telles que l'effectif relativement restreint de nos populations, qui pourrait limiter l'extrapolation des résultats. Ensuite, les résultats des corrélations en imagerie volumétrique n'apparaissaient par corrigés en FWE ni en FDR, dans l'étude sur le self-conceptuel et l'étude sur la mémoire autobiographique épisodique. De plus, nous n'avons pas pu mener d'analyses corrélationnelles en imagerie pour l'étude sur l'intéroception, du fait de la distribution non normale des résultats, nous limitant à une comparaison du degré d'atrophie entre les patients

les plus déficitaires et les moins déficitaires, dans la tâche de détection des battements cardiaques. Finalement, le regroupement des patients et des sujets témoins pour notre analyse globale du lien entre les différentes composantes du self pourrait constituer un biais méthodologique. Ainsi, nos études mériteraient d'être reproduites sur une cohorte plus importante, comparant des patients atteints de MCL prodromale avec des patients atteints d'une maladie neuroévolutive cognitive présentant un autre pattern d'atrophie au stade prodromal, tel que la MA. Dans le cadre de ces travaux de thèse, nous avions également prévu une évaluation exhaustive du self grâce à d'autres mesures, dont nous n'avons pas encore eu l'opportunité d'exploiter les résultats. Les travaux de ce manuscrit seront ainsi complétés par de futures études, telles qu'une analyse du sens subjectif de soi réflexif aux moyens d'une évaluation de l'anosognosie, une analyse de la composante sémantisée de la mémoire autobiographique, de la mémoire sémantique personnelle, et une évaluation des processus de sémantisation et d'intégration aux moyens d'une évaluation des souvenirs définissant le soi.

Pour conclure, nos travaux ont permis de montrer qu'il existerait vraisemblablement un effondrement global du self dans la MCL prodromale, en lien avec l'atteinte insulaire précoce, qui entrainerait une altération du sentiment de soi. Conformément à nos hypothèses, nous avons montré qu'il existe une atteinte du sens subjectif de soi, du self-conceptuel et des aspects épisodiques de la mémoire autobiographique dans la MCL, dont la région insulaire semble constituer un point d'ancrage. Du point de vue théorique, les résultats de nos travaux confortent l'idée que des composantes sophistiquées comme le self-conceptuel et la mémoire autobiographique reposent sur une composante élémentaire, qu'est le sens subjectif de soi. Du point de vue de l'imagerie, nous montrons que l'insula est une structure anatomique centrale dans les réseaux du self, hébergeant le sens subjectif de soi, et dont l'atteinte semble entrainer un effondrement global du self. Du point de vue de la clinique, nos études permettent de souligner l'importance de considérer le sens subjectif de soi et les composantes qui en découlent, dans l'évaluation et la prise en charge de la MCL. Ainsi, nos études pourraient ouvrir sur de nouvelles perspectives thérapeutiques visant à renforcer le self, telle que la méditation de pleine conscience, qui a été associée à des changements structurels et fonctionnels de l'insula et du cortex cingulaire antérieur (Pernet et al., 2021), y compris chez

les personnes âgées expérimentées (Chételat et al., 2017). La méditation de pleine conscience a par ailleurs montré des effets bénéfiques sur le contrôle attentionnel, les capacités socioémotionnelles et une amélioration de la connaissance de soi (Chételat et al., 2022). Une autre perspective thérapeutique pourrait impliquer des séances de stimulation magnétique transcrânienne répétitives (rTMS), qui est une technique ayant déjà montré des effets bénéfiques sur l'état de conscience, chez des patients en état végétatif (Ge et al., 2021). Dans le cadre de la MCL, une stratégie de prise en charge pourrait par exemple conjuguer des séances de méditation de pleine conscience et de stimulation magnétique transcrânienne ciblées sur l'insula, dans l'objectif d'accroitre le sentiment de soi, et par conséquent de consolider le sens subjectif de soi et renforcer les autres composantes plus élaborées, telles que le self-conceptuel et la mémoire autobiographique.

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ANNEXES

Annexe 1 : Article sur les bases neurales de la photophobie dans la maladie à corps de Lewy prodromale à légère

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ORIGINAL ARTICLE

Neural correlates of photophobia in prodromal and mild dementia with Lewy bodies

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Abstract

Background and objectives: Photophobia is a sensory disturbance provoked by light. Little is known about the association between photophobia and dementia with Lewy bodies (DLB). In this study, we aimed to identify the frequency and the neural basis of photophobia in prodromal and mild DLB.

Methods: One hundred and thirteen DLB patients, 53 Alzheimer's disease (AD) patients, 20 AD and DLB patients, 31 patients with other neurocognitive diseases (including prodromal and mild demented patients), and 31 healthy elderly controls were included in this case–control study. Photophobia was systematically looked for and compared between groups. Among a selection of 77 DLB patients, we used voxel-based morphometry (VBM) to compare those with and those without photophobia (gray matter volume; SPM12, XjView, and Matlab R2021b software).

Results: The frequency of photophobia was higher in the DLB group (47.3%) than in the other groups ($p = 0.002$). The photophobia questionnaire score was higher in the DLB group than in the AD group ($p = 0.001$). Comparison between DLB patients with and those without photophobia showed decreased gray matter in the photophobia subgroup, in the right precentral cortex, in the eyelid motor region of Penfield's homunculus ($p = 0.007$, family-wise error [FWE] corrected).

Conclusions: Photophobia is a quite frequent symptom of prodromal and mild DLB. The neural basis of photophobia in DLB involves the right precentral cortex, which could have a role in the decrease of cerebral excitability, but also the motricity of the eyelids.

KEYWORDS
Alzheimer's disease, dementia with Lewy bodies, Lewy body disease, photophobia, voxel-based morphometry

INTRODUCTION

Dementia with Lewy bodies (DLB) is a frequent neurocognitive disease with key features such as hallucinations, cognitive and alertness fluctuations, rapid eye movement (REM) sleep behavior disorder (RBD), and parkinsonism [1]. In addition to these key characteristics, other symptoms have been described, such as depression and anxiety at the behavioral level and constipation and

orthostatic hypotension at the neurovegetative level [2]. Recently, in the MEMENTO cohort study, we described new symptoms in the prodromal stage of DLB, such as rhinorrhea, sicca syndrome, and photophobia [3]; in this cohort, photophobia was present in 36.3% of patients.

Photophobia is a sensory disturbance provoked by light, and known since 1856 to be associated with the nervous system and in particular the trigeminal nerve [4]. Photophobia was first associated with ophthalmological diseases, such as lesions of the cornea, and subsequently with neurologic and neurogeriatric conditions, such as migraine [5], blepharospasm [6], and progressive supranuclear palsy (PSP) [7]. Photophobia, present in 43%–100% of PSP patients [8], appears to cause a reduction in quality of life, with an impact on outdoor activities [9]. Photophobia has been very rarely studied in other neurocognitive diseases. In a study of six patients with Alzheimer's disease and six with Parkinson's disease, photophobia was described in all patients [10]. In a larger study of 525 PD patients, the proportion of photophobia is not precisely described but visual symptoms present in 63 patients (12%) included photophobia [11]. The neural basis of photophobia is unclear. Recently, activation of the posterior thalamus by optogenetic techniques in mice has induced photophobic behavior [12]. The thalamus has already been described as affected in DLB both functionally [13, 14] and structurally [15, 16], and in particular in the pulvinar [17].

We hypothesized that DLB patients could have photophobia frequently and that it could be related to thalamic atrophy. Thus, our goal was to clarify the frequency of photophobia in DLB compared to other neurocognitive diseases, such as Alzheimer's disease (AD), and to better understand the neural basis of photophobia using voxel-based morphometry (VBM).

PARTICIPANTS AND METHODS

Study design and participants

AlphaLewyMA is a longitudinal study, whose aim is to search for biomarkers of DLB, taking place in the tertiary memory clinic named "Centre Mémoire de Ressources et de Recherche" (CM2R) of Strasbourg and Colmar, France [18]. All patients enrolled in the AlphaLewyMA study had been referred to experienced neurologists and geriatricians of the CM2R for cognitive or behavioral complaints by their specialist, their local memory clinic, or their general practitioner. Healthy elderly controls (HC) were recruited among friends and relatives of the patients or via the listing of controls of the local clinical investigation center. Patients and HC underwent the following: a standardized screening protocol including medical history, various questionnaires including one on photophobia, physical and neurological examinations, neuropsychological tests including Mini-Mental State Examination (MMSE), brain MRI, and blood and cerebrospinal fluid (CSF) collection. Features of parkinsonism were evaluated using the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III): akinesia, rigidity, and tremor at rest (rated from 0 for no symptoms to 4 for severe symptoms). Fluctuations were assessed with the Mayo Clinic fluctuations scale [19]. The Parkinson's disease-associated psychotic symptoms questionnaire was used to evaluate the presence of hallucinations [20]. RBD was evaluated using a sleep questionnaire on RBD from the publication by Gjerstad et al. [21], simplified into two questions for the patient and the caregiver: one concerning movements during sleep, the second concerning vivid dreams and nightmares. Photophobia was assessed with a three-level questionnaire (0 = normal sensitivity to light, 1 = occasional photophobia or with only certain types of light, 2 = permanent photophobia or with all types of light). Data were collected at three time points, each year during the 2-year follow-up. We considered photophobia to be present when patients responded positively to the questionnaire about photophobia at least once out of the three visits. A systematic questioning on new health problems is carried out every year, including ophthalmic diseases, with the aim to avoid bias about photophobia due to eye diseases.

Patients with prodromal DLB or DLB dementia were selected according to McKeith's criteria [1, 22]. Patients with prodromal AD or AD dementia were selected according to Dubois' criteria [23]. Patients were considered to have DLB and AD if they met both the Dubois criteria and the McKeith criteria concurrently. For example, a patient with memory storage disorders, a CSF in favor of AD, and two of the four clinical criteria for DLB was considered to have both DLB and AD. A total of 247 participants were included in this study: 110 DLB patients (DLB group), 57 AD patients (AD group), 19 DLB and AD patients (DLB + AD group), 30 diseased control patients (DC group), and 31 HC (HC group). The DC group consisted of patients originally included in the study with cognitive disorders as found in AD and DLB who, after a follow-up in the study, were found to have neither AD nor DLB. The DC group had various diagnoses, defined according to international criteria. All participants provided written informed consent for the study in accordance with the Declaration of Helsinki, and the study was approved by the Ethics Committee of East France (IV).

Neuroimaging study

We used VBM to investigate the neuroanatomical correlates of photophobia in 77 of the 110 DLB patients. These 77 patients were selected because they had participated in all three visits during the 2 years. Presence of photophobia at any time point was scored 1 and its absence was scored 0, using the photophobia questionnaire (see earlier). Each of these patients had undergone a high-resolution anatomical MRI scan at inclusion. T1-weighted three-dimensional anatomical images were obtained using a 3 T MRI scanner (Verio 32-channel Tim Siemens scanner; Siemens) using a volumetric magnetization-prepared rapid acquisition with gradient echo (MPRAGE) sequence (FOV = 256 × 256 mm^2, image matrix = 256 × 256, slice thickness = 1 mm, repetition time = 1900 ms, echo time = 2.52 ms, flip angle = 9°). VBM analyses included image preprocessing and statistical analyses. These steps were carried

out using the SPM12 software package (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/) running on Matlab R2021b (MathWorks). Anatomical MR images were spatially preprocessed using standard procedures [24]. All T1-weighted structural images were first segmented, bias-corrected, and spatially normalized to the Montreal Neurological Institute (MNI) space using an extension of the unified segmentation procedure that includes six classes of tissue. The DARTEL registration toolbox was then used to build a study-specific template and to bring into alignment all the segmentation images. The VBM analysis was done on modulated gray matter (GM) images; that is, the GM value in each voxel was multiplied by the Jacobian determinant derived from the spatial normalization. This procedure preserves the total amount of GM from the original images. These modulated GM images were smoothed with a Gaussian kernel (FWHM, 8 mm). Analyses compared DLB with photophobia and DLB without photophobia in terms of GM volume (SPM12 and XjView), including age and total intracranial volume as covariates, and thresholded at $p<0.05$ corrected (family-wise error, FWE).

Statistical analysis

The Statistical Package for Social Sciences software (SPSS v. 27.0.0.0, http://www-01.ibm.com/software/analytics/spss/) was used for further statistical evaluation as required. Where appropriate, differences in demographic and clinical data were assessed using parametric (ANOVA, *t*-tests) and nonparametric tests (Kruskall–Wallis H, Mann–Whitney U). Post-hoc analyses employed Tukey and Mann–Whitney U for ANOVA and Kruskall–Wallis tests, respectively. For categorical measures, χ^2 tests were applied. For each test statistic, a probability (p) value of <0.05 was regarded as significant.

RESULTS

Clinical results

A detailed description of the five groups is given in Table 1. The five groups were comparable in terms of educational level, gender, and handedness. The DC and HC groups were younger than the AD and DLB + AD groups; only the HC group was younger than the DLB group ($F=6.653$, $p<0.001$). The DC and HC groups had higher MMSE scores than the AD and DLB + AD groups; only the HC group had a higher MMSE score than the DLB group ($F=61.781$, $p<0.001$). The DLB and DLB + AD groups had higher rigidity UPDRS-III scores than the AD and HC groups ($F=51.150$, $p<0.001$). The DLB and DLB + AD groups had higher akinesia UPDRS-III scores than the AD and HC groups, and the DLB group had a higher score than the DC group ($F=54.148$, $p<0.001$). The DLB groups had a higher tremor UPDRS-III scores than the AD group ($F=9.876$, $p<0.043$). The Parkinson's disease-associated psychotic symptoms questionnaire score was higher in the DLB group when compared to the AD and HC groups and was higher in the DC group when compared to the AD group ($H=42.335$, $p<0.001$). The Mayo Clinic Fluctuations Scale score was higher in the DLB group than in the AD, HC, and DC groups. The RBD sleep questionnaire score was higher in the DLB group compared to the AD group but not when compared to the other groups ($H=22.780$, $p<0.001$). The number of prodromal DLB was 77, prodromal AD 29, and prodromal DLB + AD 5. ^{123}I-FP-CIT SPECT (single-photon emission computed tomography) (dopamine transporter [DAT] scan) was conducted in 45 prodromal and mild DLB patients and we found dopamine transporter loss in 31 patients.

The frequency of photophobia was higher in the DLB group (47.3%) than in the other groups (AD group, 19.3%; DLB + AD group 15.8%; DC group 30.0%; and HC group 35.5%; $p=0.002$). The photophobia questionnaire score was higher in the DLB group than in the AD group ($p=0.001$) but was not higher than in the DLB + AD group ($p=0.060$), the DC group, and the HC group (Table 1). We determined the reliability of our questionnaire by applying Cronbach's alpha for the 3 years: the alpha was 0.741. The diagnosis of patient in the DC group with photophobia status is given in Table S1. During the 2-year follow-up, in the DLB group 7 patients had ophthalmic disease: 3 patients had no photophobia (2 cataract surgeries and 1 retinal detachment), 4 patients had photophobia (1 ectropion, 2 age-related macular degeneration [AMD], and 1 chronic glaucoma); in the AD group 5 patients had ophthalmic disease: 3 without photophobia (1 AMD, 1 chronic conjunctivitis, 1 chronic glaucoma) and 2 with photophobia (1 bilateral blindness, 1 chronic uveitis); in the DLB + AD groups no patient developed eye disease; in the HC group 3 patients had ophthalmic disease all with photophobia (1 angle closure glaucoma, 1 AMD, 1 unilateral blindness); and in the DC group 1 patient with photophobia developed an ophthalmic sarcoidosis and 1 without photophobia had bilateral AMD. No keratitis, iritis, blepharitis, or blepharospasm was noted whatever the group during the 2-year follow-up.

Neuroimaging results

Of the 77 DLB patients with brain MRI, 44% had photophobia. Comparison of the DLB subgroup with photophobia and the DLB subgroup without photophobia showed decreased GM in the subgroup with photophobia, in the right precentral cortex (Brodmann area 9), in the eyelid motor region of Penfield's homunculus ($p=0.007$, FWE-corrected, $T=5.34$, $k=90$ for the peak level, and $p=0.006$, FWE-corrected for the cluster level). No other area was found with this correction. Figure 1 shows the precise localization of the precentral GM decrease.

DISCUSSION

This study confirms that photophobia exists in DLB, that it correlates clinically with the presence of hallucinations, and that structurally the difference between DLB with and without photophobia is in the precentral cortex.

TABLE 1 Clinical and demographic features of dementia with Lewy bodies patients, Alzheimer's disease patients, dementia with Lewy bodies and Alzheimer's disease patients, diseased controls, and healthy controls.

Feature		DLB ($N=110$)	AD ($N=57$)	DLB + AD ($N=19$)	DC ($N=30$)	HC ($N=31$)	Statistic test, p	Post-hoc[e]
Age, years[a]		71.4 (9.3)	74.5 (8.4)	74.8 (8.5)	67.3 (9.4)	66.0 (9.0)	$F=6.653$, $p<0.001$*	HC < DLB, AD and DLB + AD DC < AD and DLB + AD
Education[a,b]		11.9 (4.3)	12.0 (3.9)	11.7 (2.9)	12.0 (3.3)	12.7 (2.1)	$H=1.994$, $p=0.737$	
Sex (F/M)		58/52	30/27	9/10	17/13	18/13	$\chi^2=0.711$, $p=0.950$	
Handedness (R/L/A)		94/9/1	49/6/1	18/0	25/3/1	29/2	$\chi^2=4.645$, $p=0.795$	
MMSE score (/30)[a]		25.3 (3.9)	24.1 (3.3)	23.2 (3.9)	27.0 (2.8)	28.8 (1.2)	$H=61.781$, $p<0.001$*	HC > DLB + AD, AD, and DLB DC > DLB + AD, AD
Photophobia, *N* (%)		52 (47.3)	11 (19.3)	3 (15.8)	9 (30.0)	11 (35.5)	$\chi^2=16.912$, $p=0.002$*	
Photophobia questionnaire	0/1/2	58/25/27	46/9/2	16/2/1	21/3/6	20/9/2	$H=19.061$, $p<0.001$*	DLB > AD
Parkinsonism	Rigidity 0/1/2/3/4	36/59/6/1/0	34/4/1/0/0	6/6/1/0/0	16/6/1/1/0	30/1/0/0/0	$H=51.150$, $p<0.001$*	DLB > HC and AD DLB + AD>HC and AD
	Akinesia 0/1/2/3/4	39/52/11/0/0	35/3/0/0/0	7/7/1/0/0	18/3/3/0/0	30/1/0/0/0	$H=54.148$, $p<0.001$*	DLB > HC, AD, and DC DLB + AD>HC and AD
	Tremor 0/1/2/3/4	75/21/0/0/0	35/2/0/0/0	11/4/0/0/0	21/2/0/0/0	27/2/0/0/0	$H=9.876$, $p<0.043$*	DLB > AD
Hallucinations (/10)[a]		1.5 (1.9)	0.3 (0.8)	0.4 (0.7)	1.3 (2.0)	0.1 (0.3)	$H=42.335$, $p<0.001$*	DLB > HC and AD; DC > AD
Fluctuations[c]	0/1/2/3/4	19/34/30/15/6	36/7/5/0/0	6/8/1/2/0	14/7/1/2/1	22/6/1/0/1	$H=61.408$, $p<0.001$*	DLB > AD, HC, and DC
RBD	0/1/2	37/22/28	36/6/2	9/3/4	12/6/2	19/9/1	$H=22.780$, $p<0.001$*	DLB > AD
CSF[a]	Abeta-42	822.7 (291.9)	582.5 (201.6)	598.8 (241.0)	1115.5 (275.8)	–	$F=22.139$, $p<0.001$*	DLB > AD, DLB + AD; DC > AD, DLB + AD, DLB
	P-Tau	44.1 (15.2)	87.3 (30.1)	92.4 (28.7)	44.4 (12.4)	–	$F=52.146$, $p<0.001$*	DLB < AD and DLB + AD; DC < AD and DLB + AD
	Tau	292.1 (185.8)	651.9 (291.5)	622.8.6 (173.1)	287.1 (102.0)	-	$F=34.203$, $p<0.001$*	DLB < AD and DLB + AD; DC < AD and DLB + AD
Hippocampal atrophy[d] 0/1/2/3/4	Left hippocampus	33/19/22/10/4	9/11/14/7/1	1/4/7/3/2	9/6/1/0/0	16/11/2/0/0	$H=30.165$, $p<0.001$*	AD+DLB > HC and DC; AD>HC and DC; DLB > HC
	Right hippocampus	32/11/21/8/6	6/16/13/5/2	0/6/6/1/2	6/4/2/0/0	10/12/3/0/0	$H=20.225$, $p<0.001$*	AD+DLB > HC and DC; AD>HC

Abbreviations: A, ambidextrous; AD, Alzheimer's disease; CSF, cerebrospinal fluid; DC, diseased controls; DLB, dementia with Lewy bodies; F, female; HC, healthy controls; L, left; M, male; MMSE, Mini-Mental State Examination; R, right; RBD, rapid eye movement (REM) sleep behavior disorder; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

[a] Mean (SD).

[b] Education: years from primary school.

[c] Scores on the Mayo Fluctuation Scale (/4).

[d] Mean (SD, number of patients tested). According to Scheltens et al., [36].

[e] Tukey post-hoc test for ANOVA (F), Kruskall–Wallis post-hoc test on SPSS (H).

* $p>0.05$.

We showed that photophobia is quite a frequent neurosensory symptom in DLB, since it was present in 47.3% of patients. We had previously demonstrated in the MEMENTO cohort with prodromal DLB patients that the frequency of photophobia was slightly lower at 36.3% [3]. This difference may be explained by the fact that the present study included patients with mild cognitive impairment (MCI) and mild dementia, whereas the previous study included patients with subjective cognitive complaints and MCI, thus overall at an earlier stage. Moreover, photophobia is less common in AD: in the present study, the frequency was 19.3%.

Many studies suggest that photophobia in the context of migraine is characterized by diffuse associative visual cortex abnormalities, possibly linked to thalamic structures [25]. In the same way, the neural basis of visual hallucinations in DLB almost systematically includes the associative visual cortex and frequently includes the cuneus [26, 27]. The main hypothesis is that visual areas are deficient and send false information (bottom-up phenomenon), and the information is not recognized as abnormal because of a deficiency also of the frontal lobe (top-down phenomenon) [27]. Thus the visual system, including the occipital cortex, could be the link between visual hallucinations and photophobia.

However, the comparison of the two DLB subgroups with and without photophobia did not find a difference in the visual cortex but in the right precentral cortex. Several mechanisms could explain photophobia in DLB. The first one would be an impairment of the trigeminovascular system, as described in migraine [28]. The second could be related to a possible blepharospasm secondary to DLB. The third one could be related to the eye directly. Indeed, photophobia is frequently associated with disorders of the eye such as iritis, uveitis, and blepharitis [29]. No such problem was identified in the DLB group, but there was one uveitis in the AD group, and one in the DC group (sarcoidosis) during the 2-year follow-up.

We found a proportion of photophobia of 35.5% in the elderly controls. In young subjects, using a question on gene by light, the proportion is also 35% according to a study on students without migraine [30]. The lower proportion of photophobia in the DLB+AD group may be explained by the greater cognitive impairment (although not significant), or by a lesser awareness of the disorders anosognosia or anososodiaphoria, or by the fact that the association of the two diseases may modify the symptomatology, rather on the side of the disappearance of symptoms that are frequent in the healthy subject than on the side of the appearance of a symptom.

The trigeminovascular system is a complex system with first-order thalamus neurons located in the ventral posteromedial nucleus (VPM) that project to different parts of the cortex, including the primary and secondary sensory cortex and the insula [31, 32]. These projections (the so-called pain matrix) are more likely to play a role in the perception of pain, and particularly the perception of a headache in migraine [32]. Noseda et al. identified, in the posterior thalamus of rats, units of neurons that responded to the stimulation of the dura and were in the majority of cases also photosensitive [28]. The cortical projections of dura/light-sensitive neurons include the somatosensory cortex, the visual cortex, but also the primary and secondary motor cortex [28]. These cortex are part of the precentral cortex. This raises the question of a link between this motor system and the photophobia of DLB patients. Normally, the precentral cortex exhibits 20 Hz oscillatory activity that is essential for setting up proper levels of intracortical and thalamic inhibition [32]. In the context of DLB patients with photophobia, the decreased GM volume in the right precentral cortex could decrease the ability of this precentral cortex to govern cortical excitability and the activity of descending modulatory pathways. These differences between photophobia and non-photophobia have also been found in migraine patients in the premonitory phase: patients with photophobia had hyperactivation of the right precentral cortex [33].

Photophobia can also be considered as an autonomic nervous system symptom as is the case in Parkinson's disease, multiple system atrophy, or PSP [34]. It is then often associated with a pupillomotor dysfunction [8]. We described this autonomic involvement in DLB in a previous article, where we demonstrated that DLB patients also had other early neurovegetative disorders, namely rhinorrhea, sicca syndrome, and constipation [3].

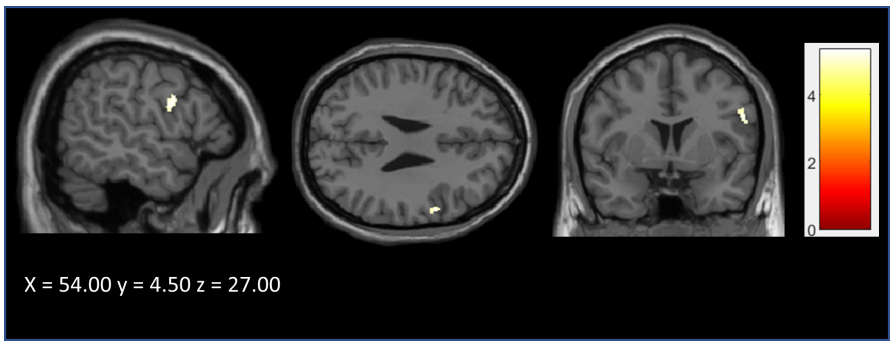

FIGURE 1 Comparison between prodromal and mild dementia with Lewy bodies patients with and without photophobia, showing decreased gray matter concentration in the right precentral cortex in the photophobia subgroup. Sagittal, axial, and coronal views. Family-wise error (FWE) corrected threshold $p < 0.05$, including age and total intracranial volume as nuisance covariates.

The precentral region on the right that we detected as being decreased in GM volume corresponds to the motor activity of the face and particularly the eyes and eyelids according to Penfield's homunculus [35]. Photophobia in DLB could therefore be related to a motor dysfunction of the face. The patients would blink less or less well, which would promote the entry of light into the orbit and therefore result in discomfort.

CONCLUSIONS

This study confirmed the existence of photophobia in almost half of the prodromal and mild DLB patients. The neural basis of photophobia in DLB involves the precentral cortex, which could have a role in the motricity of the eyelids, and the decrease of cerebral excitability. The next step will be to evaluate brain MRI microstructural and functional changes in DLB patients to determine more precisely the brain areas involved in photophobia.

AUTHOR CONTRIBUTIONS

Alice Tisserand: Writing – original draft; software; formal analysis. **Benjamin. Cretin:** Conceptualization; investigation. **Mary Mondino:** Software; formal analysis. **Anne Botzung:** Investigation; project administration. **Lea Sanna:** Project administration; formal analysis; data curation. **Catherine Demuynck:** Investigation; methodology. **Pierre Anthony:** Investigation; methodology. **Candice Muller:** Investigation; methodology. **Olivier Bousiges:** Investigation; methodology. **Nathalie Philippi:** Investigation; methodology; conceptualization. **Frederic Blanc:** Writing –original draft; software; formal analysis; Conceptualization; investigation.

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CONFLICT OF INTEREST STATEMENT

F.B. was the national coordinator for France for the Eisai Delphia (E2027), Axovant Headway-DLB and Roche Graduate clinical trials; he had received honoraria from Roche, Eisai, and Biogen for oral presentations. The other authors declare that they have no competing interests.

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DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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CONSCIENCE DE SOI ET MÉMOIRE AUTOBIOGRAPHIQUE DANS LA MALADIE À CORPS DE LEWY : ÉTUDE COMPORTEMENTALE ET EN NEUROIMAGERIE MULTIMODALE

Résumé

L'objectif de ce travail était d'étudier le self et d'en identifier les substrats neuroanatomiques aux stades débutants de la maladie à corps de Lewy (MCL), qui constitue un modèle d'étude privilégié puisqu'elle se caractérise par une diminution de volume précoce de l'insula, une région centrale dans les réseaux du self. Cette étude a confirmé qu'il existe une altération des différentes composantes du self dans la MCL, caractérisée par une atteinte de l'intéroception, qui fait partie du sens subjectif de soi, un appauvrissement des représentations de soi, qui alimentent le self-conceptuel, ainsi qu'une altération des aspects épisodiques de la mémoire autobiographique. Concernant les substrats neuroanatomiques du self, l'insula apparait comme région commune aux différentes composantes explorées, parmi d'autres régions associées. Enfin, ces travaux confirment l'existence d'un lien entre les différentes composantes du self, dont l'altération de la composante la plus élémentaire qui est le sens subjectif de soi, semblerait impacter les composantes plus élaborées que sont le self-conceptuel et la mémoire autobiographique, entrainant alors un effondrement global du self dans la MCL.

Mots clés : maladie à corps de Lewy, MCL, self, conscience de soi, mémoire autobiographique, cortex insulaire, insula, sens subjectif de soi, self-conceptuel, intéroception, neuropsychologie, IRM, VBM, volumétrie

Résumé en anglais

The aim of the present study was to investigate the self and to identify its neuroanatomical substrates in the early stages of dementia with Lewy bodies (DLB), which serves as a privileged study model, as DLB is characterized by an early insular atrophy, a central region within the self networks. This study confirmed that there is an alteration of the different components of the self in DLB, characterized by impairments of interoception capacities, which are part of the subjective sense of self, an impoverishment of self-representations that feed into self-concept, as well as an alteration of the episodic aspects of autobiographical memory. Regarding the neuroanatomical substrates of the self, the insula appears as a region common to the different explored self components, among other associated regions. Finally, these findings confirm the existence of a link between the different components of the self, including the alteration of the most elementary component, which is the subjective sense of self, which seems to impact the more elaborated ones, such as the self-concept and autobiographical memory, thus leading to a global collapse of the self.

Keywords: dementia with Lewy bodies, DLB, self-consciousness, self-awareness, autobiographical memory, insular cortex, insula, subjective sense of self, self-concept, interoception, neuropsychology, MRI, VBM, volumetry