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Apathy in late-life depression: new biomarkers using actimetry and magnetic resonance imaging

Jean-Charles Roy

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L'UNIVERSITE DE RENNES

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Sciences de la Vie et de la Santé
Spécialité : *Neurosciences / Ethologie*

Par

Jean-Charles ROY

Apathy in Late-Life Depression: New Biomarkers using Actimetry and Magnetic Resonance Imaging

Thèse présentée et soutenue à Rennes, le 21/11/2023
Unité de recherche : Empenn U1228

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List of acronyms

ACC:	Anterior cingulate cortex
AES:	Apathy evaluation scale
AMI:	Apathy motivation index
COI:	Component of interest
dACC:	Dorsal anterior cingulate cortex
DCA:	2018 Diagnostic Criteria for Apathy
DLPFC:	Dorso-lateral prefrontal cortex
DRS:	Mattis dementia rating scale
DSM-5:	Diagnostic and Statistical Manual of Mental Disorders, fifth version
DTI:	Diffusion Tensor Imaging
EPI:	Echo-planar imaging
FA:	Fractional Anisotropy
fMRI:	functional magnetic resonance imaging
FOV:	Field-of-view
FSL:	FMRIB software library
FWE:	Family-wise error
HC:	Healthy control
LLD:	Late-life depression
MADRS:	Montgomery-Asberg depression rating scale
MCST:	Modified card sorting test
MD:	Mean Diffusivity
MINI:	Mini-international neuropsychiatric interview
NBS:	Network Based Statistic
NODDI:	Neurite orientation dispersion and density imaging
ODI:	Orientation Dispersion Index
PCA1:	first principal component of motor activity
PCA2:	second principal component of motor activity
ROI:	Region of interest
RSN:	Resting State Network
rsFC:	Resting-state functional connectivity
TE:	Echo time
TI:	Inversion time
TFNBS:	Threshold-free network-based statistics
TMT-A:	Trail A of the Trail Making test
TMT B-A:	Difference in scores between versions B and A of the Trail
TR:	Repetition time

Part I

Introduction

Chapter 1

Introduction

1.1 Context

Apathy is a known risk factor of persistent depression and of major cognitive disorder in older adults. Understanding its physiopathology would help to better diagnose and treat these patients. However, studying apathy in the context of late-life depression (LLD) raises several challenges.

Firstly, there is ambiguity surrounding the precise definition of LLD. While it can pragmatically be defined as the presence of a major depressive disorder according to the DSM-5 criteria after the age of 60 or 65 years old, this categorization encompasses a broad range of clinical expressions. This variability is further complicated by the fact that older adults often have comorbid conditions that can affect their cognitive and emotional well-being. Symptoms such as fatigue, pain, or attentional deficits can either directly manifest themselves as depressive symptoms or trigger a psychological reaction, making it challenging to disentangle the underlying causes of depression in this population. Second, apathy, as a transdiagnostic entity, is also difficult to conceptualize. Differences in theories on the exact nature of goal-directed processes, such as between the determinants and components of motivated behavior, pose questions on what can be part of apathy.

The complexity encountered in practice for defining LLD and apathy mirrors the complexity of the underlying brain mechanisms involved in these conditions. Factors such as vascular microlesions in the white matter, neuroinflammatory lesions, neurodegeneration, and functional dysconnectivity all contribute to the development of LLD. A promising approach in modeling apathy has been to conceptualize it as a reduction of goal-directed behavior and identify the specific brain regions involved in these behaviors. This approach has found support across various neurological disorders, where consistent brain lesions and impaired metabolisms have been identified in the same regions associated with goal-directed behaviors.

The motivation behind the thesis is to gain a deeper understanding of how apathy can be measured in LLD and to provide new insights into its measurement and neural correlates. To achieve this, the thesis aims to investigate the relationship between apathy in LLD and the resting-state intranetwork functional connectivity of brain regions responsible for goal-directed behaviors. This investigation incorporates three complementary apathy scales: the classical apathy evaluation scale (AES), which assesses cognitive, emotional, and behavioral dimensions of apathy; the apathy motivation index (AMI), which adds a social dimension to apathy assessment; and the 2018 diagnostic criteria for apathy, which categorizes apathy based on its functional impact.

Furthermore, the thesis seeks to explore the connection between individual variations in diurnal motor activity and apathy. This involves studying the association between principal components of motor activity recorded by actimetry and the three apathy scales. Finally, the study integrates motor and apathy measures with structural and resting-state functional connectivity data obtained through magnetic resonance imaging (MRI).

1.2 Organization and Contribution of this Thesis

This thesis is organized in four parts. The Background part reviews the theoretical and empirical framework surrounding apathy in LLD as well as the tools used to measure apathy and its relationship with brain. Then, the Materials and Methods part describes the study we conducted; it presents the objective and hypotheses of the study, as well as its design, and the method used to process MRI connectivity and actimetry. The Clinical Studies part reports the main contributions of this work for characterizing apathy in LLD and its measure via motor activity. Finally, the General Discussion reviews the main findings, limitation and perspectives.

Part I: Background

The Background part reviews the theoretical framework surrounding apathy and the epidemiological burden associated to apathy in late-life depression.

Chapter 2 answers the following question: how do we conceive apathy? This chapter covers the current conceptions of apathy, their theoretical suppositions, the subsequent measurement tools developed and the underlying goal-directed model. Despite variability in the conceptions, apathy is recognized as a transdiagnostic entity encountered in psychiatric and neurologic conditions. A consensual model considers apathy as a dysfunction of cognitive processes underlying goal-directed behaviors. These processes involve prefrontal cortical regions encoding for valued decision making along an anteroposterior gradient from valuation system to the effective realization of behavior, impaired in apathy. While clinical scales of apathy diverge in the construct they assess, due to their partial exploration of apathy, less theoretically-committed and more objective measures of ecological activity might help supporting a comprehensive study of apathy.

Chapter 3 answers the following question: why studying apathy in late-life depression? This chapter reviews the current challenges for clinicians and researchers pertaining to apathy and LLD, namely: the pejorative course associated with apathy and the complexity of its pathophysiology. Apathy is a frequent syndrome in LLD, poorly responding to treatment and associated with a significant risk of persistent depression, cognitive decline and mortality. Although few studies have investigated this entity in LLD, brain imaging studies tend to converge on abnormal connectivity between regions implied in goal-directed behaviors, notably in motivation and executive functions. Three complementary pathophysiological models propose to explain these abnormalities: a neurofunctional account of default of adaptive switching of the salience network, a neurovascular model explaining tissue lesions, and a neuroinflammatory model explaining dopamine depletion. We observed a lack of brain imaging evidence characterizing apathy behaviors and dysconnectivity in LLD, compared to the current scientific interest on goal-directed behaviors.

Part II: Materials and Methods

The Materials and Methods part describes the methodological choices we made to explore the association between apathy, brain connectivity and actimetry.

Chapter 4 asks the following question: Can apathy in late-life depression be characterized as a deficit of goal-directed behaviors? We expose the aims of the thesis which are (i) to relate different apathy measures to functional brain connectivity, (ii) to evaluate the relationship between motor activity

to apathy measures and (iii) to relate motor activity to resting-state functional and structural connectivity.

Chapter 5 presents the design and materials of the study. In a cross-sectional study, 42 LLD patients and 26 healthy controls of the same age were recruited from the French old-age psychiatry centers of Rennes and Tours. Inclusion and exclusion were assessed by a trained old-age psychiatrist. Inclusion criteria were patients aged 60 years old and DSM-5 criteria of major depressive disorder. Exclusion criteria were major cognitive disorders, significant diseases impacting on physical activity, antipsychotic medication, high suicidal risk or MRI contraindications. At inclusion, LLD subjects had a psychiatric evaluation wherein apathy was evaluated by three valid and complementary evaluations of apathy. After the evaluation, participants were required to wear a wrist actimeter during 4 days. The last day of the wearing, participants underwent a resting-state functional and diffusion-weighted MRI scan.

Chapter 6 details the preprocessing steps of MRI data for denoising and for registering atlas from MNI-space to native space. The selection of the regions of interest were made from the Human Connectome Project multimodal atlas from which resting-state networks were identified according to the Cole-Anticevic atlas. We present the network-based statistic approach, a non-parametric powerful statistical method, which enables to identify subnetworks whose connectivity is associated with a variable of interest. The main drawback of this method is the arbitrary choice of the significant threshold. We thus chose to use the threshold-free network-based statistic which calculates an adaptive threshold to correct for multiple comparisons due to the number of nodes.

Chapter 7 details the method we performed for pre-processing actimetric data, estimating individual smoothed motor activity from the 3-day recordings by generalized additive models, and predicting the functional principal component analysis of motor activity of individual participants.

Part III: Clinical Studies

The Clinical Studies part details the protocol of the study, the association between apathy and brain connectivity, the association between apathy and motor activity, and the association between motor activity and brain connectivity.

Chapter 8 answers the following questions: what are the relationships between apathy and intranetwork resting-state connectivity? And how does intranetwork resting-state connectivity vary as a function of the apathy scales? We present the results of our study pertaining to apathy clinical scales and functional connectivity. This study found that 3 apathy measurements were associated with modified intra resting-state network connectivity in key networks implied in goal-directed behaviors. The apathy scale related to social apathy, the AMI, showed stronger associations with the cingulo-opercular and frontoparietal networks, whereas the AES had stronger associations with the default mode network and the goal-oriented behavior network. Our findings indicate that apathy in LLD is consistently associated with changes in both intranetwork resting-state connectivity and internetwork resting-state connectivity of brain regions implicated in goal-oriented behaviors with some specificities between the scales. This study has been published in *Journal of Psychiatry & Neurosciences* (In press, doi:10.1503/jpn.230008).

Chapter 9 answers the following question: what are the relationships between motor activity, apathy and the underlying brain connectivity in LLD? We found that two principal components of motor activity were significantly associated with apathy. The first principal component (PCA1), corresponding to overall diurnal motor activity, was negatively associated with AES scores while the

second principal component (PCA2), corresponding to early chronotype, was negatively associated with AMI scores. Regarding intra-network resting-state functional connectivity, PCA1 was associated with increased connectivity within the default-mode, the cingulo-opercular and the frontoparietal network, while PCA2 was associated with more heterogenous connectivity between both hemispheres in the same regions. However, we did not find significant associations between microstructural metrics of white matter and patterns of motor activity. Taken together, these innovative results suggest that motor activity patterns and their associated functional neural connectivity play a pivotal role in understanding the complex interplay between apathy and LLD.

Part IV: General Discussion

Chapter 10 reviews the main results of the study, the limitation and perspectives. We found that apathy evaluations shared modifications of functional connectivity in the DMN and in the FPN, reflecting reduced emotion regulation and dysexecutive function. We found two motor activity patterns associated with apathy in late-life depression: a reduced overall diurnal activity and a late-chronotype pattern. We argue that reduced overall activity is linked to apathy severity and risk of dementia while late-chronotype is more specific to social apathy in depression. The limitation of the study pertains to the small sample size, the cross-sectional design and short recording period limit the assessment of activity patterns, the inclusion of both late-onset and early-onset depressed individuals, as well as the caution in interpreting intranetwork resting-state functional connectivity. We discuss how future perspective, combining multimodal brain imaging, multimodal behavioral recordings could help to improve current models of apathy in LLD for better diagnosis and monitoring.

Appendix

It presents the supplementary materials of the study 1 presented in **Chapter 8**. The supplementary results presented are: the quality control of MRI data, the differences in resting-state intranetwork connectivity between late-life depression and healthy control, the assessment of heterogeneity between apathy scales, the subnetworks associated with apathy adding MADRS as covariate. For the supplementary materials of study 2, presented in **Chapter 9**, we report the MRI acquisitions methods, preprocessing steps and MRI analyses, as well as the model selection of actimetry smoothing functions.

Chapitre 1

Introduction

1.1 Contexte

L'apathie est un facteur de risque connu de dépression et de trouble cognitif majeur chez les personnes âgées. Comprendre sa physiopathologie permettrait d'améliorer le diagnostic et le traitement des sujets âgés souffrant de dépression. Cependant, l'étude de l'apathie dans la dépression du sujet âgé (DSA) soulève plusieurs enjeux.

Tout d'abord, il existe une ambiguïté entourant la définition précise de la DSA. Bien qu'une définition pragmatique la considère comme la présence d'un trouble dépressif majeur selon les critères du DSM-5 après l'âge de 60 ou 65 ans, cette catégorisation englobe un large éventail d'expressions cliniques. Cette variabilité est aussi accentuée par la fréquence des comorbidités chez les personnes âgées pouvant affecter leur bien-être cognitif et émotionnel. Des conditions telles que la fatigue, la douleur ou des symptômes cognitifs peuvent se manifester directement sous forme de symptômes dépressifs ou déclencher une réaction psychologique à leurs conséquences, ce qui rend difficile la distinction des causes sous-jacentes de dépression dans cette population. Deuxièmement, l'apathie, en tant qu'entité transdiagnostique est également difficile à conceptualiser. Les différences entre théories sur la nature exacte des processus dirigés vers un but, telles que la distinction entre les déterminants du comportement motivé et les composants du comportement motivé, soulèvent des questions sur les pathologies pouvant être rapportées à l'apathie. Ce fait est illustré par la variété d'outils d'évaluation de l'apathie existant et par le nombre de dimensions cliniques qu'ils explorent.

La complexité rencontrée dans la pratique pour définir la DSA et l'apathie fait écho à la complexité des mécanismes cérébraux sous-jacents à cette pathologie. Des facteurs tels que les microlésions vasculaires de la substance blanche, les lésions neuroinflammatoires, la neurodégénérescence et la dysconnectivité fonctionnelle contribuent tous au développement complexe de la DSA. Une approche prometteuse pour comprendre l'apathie consiste à la comprendre comme une réduction des comportements dirigés vers un but et à identifier les régions cérébrales spécifiques impliquées dans ces comportements. Cette approche a permis d'unifier un grand nombre d'observations faites dans divers troubles neurologiques, où des lésions cérébrales et des métabolismes altérés ont été identifiés dans les mêmes régions associées aux comportements dirigés vers des objectifs.

La motivation de cette thèse est de mieux comprendre l'apathie dans la dépression du sujet âgé et de fournir de nouvelles perspectives sur sa mesure et ses corrélats cérébraux. Pour ce faire, la thèse vise à examiner la relation entre l'apathie dans la DSA et la connectivité fonctionnelle à l'intérieur des réseaux de repos sous-tendant les comportements dirigés vers un but. Cette enquête intègre trois échelles d'apathie complémentaires : l'apathy evaluation scale (AES), qui évalue les dimensions cognitives, émotionnelles et comportementales de l'apathie ; l'apathy motivation index (AMI), qui considère une dimension sociale à l'évaluation de l'apathie ; et les critères diagnostiques d'apathie de 2018, qui catégorisent l'apathie en fonction de son impact fonctionnel.

Enfin, cette thèse vise aussi à explorer le lien entre les variations individuelles d'activité motrice diurne et l'apathie. Pour cela, nous avons estimé l'association entre des composantes principales de l'activité motrice enregistrées par des actimètres et les trois échelles d'apathie. L'étude intègre les mesures motrices et d'apathie avec la connectivité cérébrale fonctionnelle et structurelle obtenues par imagerie par résonance magnétique (IRM).

1.2 Organisation et Contribution de la Thèse

Cette thèse est organisée en quatre parties. La première partie, intitulée "Contexte", passe en revue le cadre théorique et empirique entourant le concept d'apathie dans la DSA, les outils de mesure d'apathie utilisés et les modèles neurocognitifs associés. Ensuite, la deuxième partie, "Matériel et Méthodes", décrit les objectifs et hypothèses de l'étude, son déroulé ainsi que la méthode utilisée pour traiter les données de connectivité par IRM et actimétrie. La partie "Etudes cliniques" expose les principales contributions de ce travail pour caractériser l'apathie dans la DSA et sa capture par l'activité motrice. La quatrième partie est une discussion générale, synthétisant les résultats principaux des études, leurs limites et les perspectives en termes de mesure et compréhension de l'apathie dans la DSA

Partie I : Contexte

La partie Contexte examine le cadre théorique entourant l'apathie et la charge épidémiologique associée à l'apathie dans la dépression tardive.

Chapitre 2 répond à la question suivante : comment concevons-nous l'apathie ? Ce chapitre aborde les conceptions actuelles de l'apathie, leurs suppositions théoriques et conséquences en termes de mesure, ainsi qu'un modèle commun de troubles des comportements dirigés vers un but. Malgré la variabilité des conceptions, l'apathie est reconnue comme une entité transdiagnostique rencontrée dans les conditions psychiatriques et neurologiques. Un modèle consensuel considère l'apathie comme un dysfonctionnement des processus cognitifs liés aux comportements dirigés vers des objectifs. Ces processus impliquent des régions corticales préfrontales responsables de la prise de décision valorisée le long d'un gradient antéro-postérieur du système de l'évaluation de la valeur d'un stimulus à la réalisation effective d'un comportement adapté, qui sont altérées dans l'apathie. Bien que les échelles cliniques de l'apathie divergent dans le construit qu'elles évaluent en raison de leur exploration partielle de l'apathie, des mesures plus objectives de l'activité écologique des patients, moins engagées théoriquement, pourraient contribuer à soutenir une analyse plus intégrative de l'apathie.

Chapitre 3 répond à la question suivante : pourquoi étudier l'apathie dans la DSA ? Ce chapitre examine les défis actuels auxquels sont confrontés les cliniciens et les chercheurs en ce qui concerne l'apathie dans la DSA : le cours péjoratif associé à l'apathie dans la DSA et la complexité de sa physiopathologie. L'apathie est un syndrome fréquent dans la DSA, peu réactif au traitement et associé à un risque significatif de dépression persistante, de déclin cognitif et de mortalité. Bien que reposant sur peu d'études, les études d'imagerie cérébrale tendent à converger vers une connectivité anormale des régions impliquées dans les comportements dirigés vers un but, notamment dans la motivation et les fonctions exécutives. Trois modèles physiopathologiques complémentaires proposent d'expliquer ces anomalies : un modèle fonctionnel de perte de la fonction d'aiguillage du réseau de la saillance, un modèle neurovasculaire expliquant les lésions tissulaires observées, et un modèle neuro-inflammatoire supposant une déplétion de la dopamine. Il existe peu de données caractérisant les relations entre apathie et dysconnectivité cérébrale dans la DSA, par rapport à l'intérêt scientifique actuel portés aux comportements dirigés vers un but.

Partie II : Matériels et méthodes

La partie Matériels et méthodes décrit les choix méthodologiques que nous avons faits pour explorer l'association entre apathie, connectivité cérébrale et activité motrice.

Chapitre 4 pose la question suivante : l'apathie dans la dépression tardive peut-elle être caractérisée comme un déficit de comportements dirigés vers un but ? Nous exposons les objectifs de la thèse visant (i) à relier différentes mesures d'apathie à la connectivité cérébrale fonctionnelle, (ii) à évaluer la relation entre l'activité motrice et les mesures de l'apathie, et (iii) à relier l'activité motrice à la connectivité cérébrale fonctionnelle et structurale en état de repos.

Chapitre 5 présente le dérouler de l'étude ainsi que le matériel utilisé. Il s'agit d'une étude transversale, dans laquelle 42 patients atteints de DSA et 26 sujets contrôles du même âge ont été recrutés dans des centres de psychiatrie de Rennes et de Tours. Les critères d'inclusion et d'exclusion ont été évalués par un psychiatre de la personne âgée. Les critères d'inclusion étaient un âge supérieur ou égal à 60 ans et des critères DSM-5 de trouble dépressif caractérisé pour les patients. Les critères d'exclusion étaient la présence d'un trouble cognitif majeur, de pathologies influant sur l'activité physique tels que des troubles neurologiques ou rhumatologiques, les médicaments antipsychotiques, un risque suicidaire élevé ou des contre-indications à l'IRM. À l'inclusion, les sujets atteints de DSA ont eu une évaluation psychiatrique dans laquelle l'apathie a été évaluée par trois outils valides et complémentaires d'apathie. Après l'évaluation, les participants ont dû porter un actimètre au poignet pendant 4 jours. Le dernier jour du port, les participants ont bénéficié d'une IRM fonctionnelle de repos et d'une IRM de diffusion.

Chapitre 6 détaille les étapes de prétraitement des données d'IRM à savoir la réduction du bruit et le recalage de l'atlas cérébrale d'un espace de référence à l'espace natif des participants. La sélection des régions d'intérêt a été effectuée à partir de l'atlas de l'Human Connectome Project, et nous avons identifié les réseaux en état de repos correspondants selon l'atlas de Cole-Anticevic. Nous présentons l'approche par network-based statistic, une méthode statistique non-paramétrique puissante qui permet d'identifier les sous-réseaux dont la connectivité est associée à une variable d'intérêt. Le principal inconvénient de cette méthode est le choix arbitraire du seuil de significativité statistique. Nous avons donc choisi d'utiliser une extension de cette méthode, la threshold-free network-based statistic, qui impose un seuil adaptatif à la méthode précédente permettant de corriger pour les comparaisons multiples dues au nombre de nœuds considérés.

Chapitre 7 répond à la question suivante : comment modéliser les schémas individuels d'activité motrice ? Ce chapitre détaille la méthode que nous avons utilisée pour le prétraitement des données d'actimétrie, estimées à partir d'enregistrements d'une durée de 4 jours par des modèles additifs généralisés. À partir des prédictions du modèle sélectionné, une analyse en composantes principales fonctionnelles de l'activité motrice des participants a été réalisée et les scores des composantes individuelles ont été calculés.

Partie III : Études Cliniques

La partie Études Cliniques détaille le protocole de l'étude, l'association entre apathie et connectivité cérébrale, l'association entre apathie et activité motrice, ainsi que l'association entre activité motrice et connectivité cérébrale.

Chapitre 8 répond aux questions suivantes : quelles sont les relations entre l'apathie et la connectivité intra-réseau dans à l'état de repos et comment cette connectivité varie en fonction des échelles d'apathie utilisées ? Nous présentons les résultats d'une étude s'étant intéressée aux associations entre les échelles cliniques de l'apathie et la connectivité fonctionnelle. Cette étude a révélé que trois mesures de l'apathie étaient associées à une connectivité intra-réseau de repos modifiée dans les réseaux clés impliqués dans les comportements dirigés vers un but. L'apathie sociale, mesurée par l'échelle AMI, retrouvait des associations plus marquées avec les réseaux cingulo-operculaire et fronto-pariétal, tandis que l'AES présentait des associations plus marquées avec le réseau du mode par défaut et le réseau du comportement dirigé vers un but. Nos résultats indiquent que l'apathie dans la DSA est

systématiquement associée à des changements de connectivité cérébrale à l'état de repos dans les régions cérébrales impliquées dans les comportements orientés vers un but, avec des spécificités entre les échelles. Cette étude a été publiée dans *Journal of Psychiatry & Neurosciences* (doi:10.1503/jpn.230008).

Chapitre 9 répond à la question suivante : comment identifier les relations entre activité motrice, apathie et connectivité cérébrale associée à la DSA ? Nous présentons les résultats de notre étude concernant les patterns d'activité motrices associés à l'apathie et leur relation avec la connectivité fonctionnelle. Dans cette étude, nous avons trouvé deux composantes principales d'activité motrice significativement associées à l'apathie. La première composante principale, correspondant à l'activité motrice diurne globale, était négativement associée aux scores de l'AES, tandis que la deuxième composante principale, correspondant à un chronotype précoce, était négativement associée aux scores d'AMI. En ce qui concerne la connectivité fonctionnelle en état de repos intra-réseau, la première composante principale était associée à une connectivité accrue au sein du réseau du mode par défaut, du réseau cingulo-operculaire et du réseau frontopariétal, tandis que la seconde composante principale était associée à une connectivité plus hétérogène entre les hémisphères de mêmes régions. Cependant, nous n'avons pas trouvé d'associations significatives entre les mesures microstructurales de la substance blanche et les patterns d'activité motrice. Dans l'ensemble, ces résultats innovants suggèrent que les patterns d'activité motrice et leurs connectivités cérébrales fonctionnelles associées jouent un rôle essentiel dans la compréhension de l'interaction complexe entre l'apathie et la DSA.

Partie IV : Discussion Générale

Chapitre 10 reprend les résultats principaux des études, les limites et perspectives futures. Nous trouvons que l'ensemble des évaluations d'apathie partagent des modifications de connectivité fonctionnelle dans le réseau par défaut et dans le réseau frontopariétal, reflétant une régulation émotionnelle réduite et une atteinte des fonctions exécutives. Nous avons identifié deux profils d'activité motrice associés à l'apathie dans la dépression du sujet âgé : une réduction globale de l'activité diurne et un chronotype tardif. Nous argumentons que la réduction globale de l'activité serait liée à la sévérité de l'apathie et au risque de démence, tandis que le chronotype tardif est plus spécifique à l'apathie sociale dans la dépression. Les limitations de l'étude concernent la petite taille de l'échantillon, la conception transversale et la courte période d'enregistrement limitant l'évaluation des profils d'activité, l'inclusion de dépression de début tardif et précoce, ainsi que la prudence dans l'interprétation de la connectivité fonctionnelle en repos intra-réseau. Nous discutons les perspectives futures permettant d'améliorer les modèles actuels d'apathie dans la DSA. La combinaison d'imagerie cérébrale multimodale ainsi que d'enregistrements multimodaux du comportement permettraient d'améliorer le diagnostic des patients à risque et améliorer leur surveillance

Annexe

L'annexe 1 présente les matériels supplémentaires de l'étude présentée dans le **chapitre 8**. Les résultats supplémentaires comprennent : le contrôle qualité des données IRM, les différences de connectivité intraréseau à l'état de repos entre la dépression tardive et les sujets contrôle, l'évaluation de l'hétérogénéité entre les échelles d'apathie, les sous-réseaux associés à l'apathie en ajoutant le MADRS en covariable.

Pour les matériels supplémentaires de l'étude 2, présentés dans le chapitre 9, nous rapportons les méthodes d'acquisition par IRM, les étapes de prétraitement et les analyses IRM, ainsi que le résultat de la sélection du modèle des fonctions de lissage d'actimétrie.

Part II

Background

Chapter 2

Modeling Apathy: Theoretical Framework, Measurement tools and Brain Underpinnings

OVERVIEW

How do we conceive apathy? This chapter aims at giving context on the model of apathy chosen in this thesis. It covers the current conceptions of apathy, their theoretical suppositions, their consequences in terms of measurement and the underlying goal-directed model. Overall, this introductory chapter is inspired from original and review articles from Marin (1991), Brown and colleagues (2000), Lévy & Dubois (2006), Robert et al. (2009), Le Héron and colleagues (2018), Husain & Roiser (2018) and Dickson & Roiser (2022).

2.1 The Construct of Apathy

Conventionally, apathy is defined as the absence or lack of feeling, emotions, interest, or concern. The term “apathy” emerged in medical scientific context in the early 19th century, referring to states of psychological and physical loss of reactivity, associated with severe prognoses in diverse medical conditions (Bettoni, 1822; Dechambre, 1883). While having provided evidence for a dissociation between the behavioral lack of reactivity in parkinsonian patients, compared to their persevered mental functioning or absence of impaired emotions, the term of apathy appeared in psychiatry before the neurologist Brissaud. Guislain applied this term to designate an incurable state of loss of reactivity complicating untreated mental disorders (Guislain, 1852). Apathy was later related to morbid emotiveness, understood as a loss of representation of emotional states related to an object, observed typically after an exhaustion of the patients by nervous or physical stress (Féré, 1892). The term of apathy was less used in subsequent years in psychiatry, preferentially replaced by more precise concepts committed to psychopathological theories such as abulia, avolition, anergia, anhedonia or athymhormia. In the early 1990s, Marin provided a major attempt to define apathy as a syndrome, corresponding to a lack of motivation not attributable to disturbance of intellect, emotion, or level of consciousness (Marin, 1991a). If loss of motivation is attributable to disturbance of intellect, emotion, or level of consciousness, apathy is considered a symptom. In this formulation, apathy is considered to exist in three potentially dissociable components of goal-directed behavior: diminished productivity (behaviors), diminished goals (cognition), and diminished emotional responses to success or failure (emotions). The author emphasizes the importance to distinguish apathy from depression as apathetic patients are not necessarily depressed; more than depressed patients cannot be apathetic.

A second influential conceptual framework is Levy & Dubois’ model of apathy (R. Levy & Dubois, 2006). They defined apathy as a quantitative reduction of self-generated voluntary and purposeful behaviors, following the goal-directed behavior (GDB) model (Brown & Pluck, 2000). The construct of GDB was developed in the 1980s and gain great conceptual development during the 1990s on a cognitive and neuroanatomical points-of-view. This model conceives GDB as a set of organized processes by which an internal state is translated, through action, into the attainment of a represented goal. From this model and with the neuroscientific knowledge at disposal, Levy & Dubois proposed three domains of apathy: cognitive, emotional-affective and autoactivation (Levy & Dubois, 2006). All of these domains are related to putative brain mechanisms. One notable difference with Marin’s

account, is that the authors replace “motivation” by “goal-directed behavior”; the latter being easier to objectify. Also, they mention that depression could produce apathy by an alteration of emotional-affective system.

The model was lately refined by adding a social domain to apathy (Ang et al., 2017; Sockeel et al., 2006; Stuss et al., 2000), understanding self and social awareness as “a metacognitive ability, necessary to mediate information from a personal, social past and current history with projections to the future” (Stuss et al., 2000). Radakovic & Abrahams (2018) proposed to incorporate this social domain to Levy & Dubois’ model of apathy. In their framework, initiation apathy is related to energization, pertaining to the arousal and maintenance aspects of motivation, executive apathy related to executive functions such as cognitive control, and emotional apathy to emotional self-regulation. The authors also postulate that a self-awareness component operates across all apathy dimensions.

2.2 Measurements Tools of Apathy

Apathy scales

With the development of these conceptual frameworks, specific apathy scales have been developed, summarized in **Table 1**.

The Apathy Evaluation Scale (AES) is the earliest assessment method (Marin et al., 1991b), measuring apathy along cognitive, behavioral, and emotional dimensions. The Apathy Evaluation Scale, is a semi-structured interview which evaluates apathy from the patient’s reported interests, activities and daily routine during the four last weeks. This scale has inspired different evaluations with similar structures. Among these tools, the Apathy Scale is a 14-item abridged version of the AES having six items in common with it, primarily measuring cognitive and behavioral apathy (Starkstein et al., 1992). The Apathy Inventory consists of one item each for cognitive, behavioral, and emotional apathy (P. H. Robert et al., 2002). By contrast, the Lille Apathy Rating Scale is an extension of the AES, comprising 33-items across nine domains which are lack of interest, extinction of novelty seeking, reduced motivation, lack of concern, poor social life, reduction in everyday productivity, lack of initiative and blunted emotional response (Sockeel et al., 2006).

Levy & Dubois’ account on apathy is a theoretical view based on cognitive neuroscience. The first empirical test of this framework was the Dimensional Apathy Scale (Radakovic & Abrahams, 2014). The DAS has 24 items covering executive, (behavioral/cognitive) initiation, and emotional dimensions of apathy. As noted in Dickson & Husain (2022), the executive dimension of apathy captures most of the variance in factor analysis of the items in the DAS. While possibly identifying a process producing apathy, the emphasis on executive function in apathy is challenged by Marin’s conception as a loss of interest.

Several other independent apathy scales have also been developed. The Apathy Motivation Index (AMI) (Ang et al., 2017) is an 18-item self-report questionnaire which assesses apathy in terms of Behavioral Activation (tendency to self-initiate goal-directed behavior), Emotional Sensitivity (affective responses) and Social Motivation (level of engagement in social interactions). It uses a 5-point Likert scale with higher scores indicating more severe apathy. Other scales have also been developed for use in specific populations, such as the Apathy in Institutionalised Persons with Dementia (Lancôt et al., 2017), which follows a triadic structure including deficits of thinking and self-generated behavior, cognitive inertia and emotional blunting. The Pearson Environment Apathy Rating (Jao et al., 2016) consists of an Environment subscale, examining the relationship between apathy and the environment, and an Apathy subscale, assessing facial expression, eye contact, physical engagement, purposeful activity, verbal tone and verbal expression. In addition, an assessment of apathy is also made, albeit in only one general syndromic dimension, in broader clinical tools such as the Neuropsychiatric Inventory (Cummings et al., 1994) or the Frontal Systems Behavior Scale (Grace et al., 1999).

Apathy scales	Administration	N-items	Domains assessed
<i>Multidimensional</i>			
Apathy Evaluation Scale (AES-S/I/C) Marin et al. (1991)	AES-S: self-report AES-I: informant based AES-C: clinician administered	18-items	
Apathy Scale (AS) Starkstein et al. (1992)	Self-report, informant, and clinician administered	14-items	
Apathy Inventory (IA) Robert et al. (2002)	Self-report and informant versions	3-items	
Irritability Apathy Scale (IAS) Burns, Folstein, Brandt, and Folstein (1990)	Informant interview	5-items	
Apathy in Institutionalised Persons with Dementia (APADEM-NH) Lancôt et al. (2017)	Informant interview	26-items	
Lille Apathy Rating Scale (LARS) Sockeel et al. (2006)	Self-report/patient interview, Caregiver based	33-items	
Dimensional Apathy Scale (DAS) Radakovic and Abrahams (2014)	Self-report	24-items	
Apathy Motivation Index (AMI) Ang et al. (2017)	Self-report	18-items	
Pearson Environment Apathy Rating (Jao et al., 2016)	Clinician observation	12-items	
<i>Unidimensional</i>			
Neuropsychiatric Inventory (NPI) Cummings et al. (1994)	Patient/informant interview	16-items	
Frontal System Behaviour Scale (FrSBe) Grace et al. (1999)	Self-report, informant-based, clinician interview	46-items, 14 for apathy	
Dementia Apathy Rating Scale (DAIR) Strauss and Sperry (2002)	Informant interview	1-item for apathy answerable by "yes" or "no". Follow-up questions on frequency and severity of symptom asked if response is "yes".	

Table 1. Summary of apathy scales and the dimensions assessed (Dickson & Roiser, 2022)

Diagnostic criteria

In 2008 the European Psychiatric Association recognized the need for apathy diagnostic criteria specific to neurodegenerative diseases. The resulting criteria required apathy to be diagnosed based on a loss or diminished motivation and the presence of at least one symptom in at least two of three domains of apathy (reduced goal-directed behavior, goal-directed cognitive activity, or emotions). Those criteria also stated that the symptoms must result in clinically significant impairment and not be explained by other possible causes, such as physical disabilities, change in level of consciousness, or the effect of a substance. Since then, there have been considerable advances in apathy research. In recognition of these progresses, an international consensus group of 23 experts was constituted in 2018 to operationalize the criteria for apathy (Robert et al., 2018, **Table 2**). First, a quantitative reduction of goal-directed activity in comparison to the patient's previous level of functioning must be observed. Second, symptoms must persist for at least four weeks and affect at least two of the three apathy dimensions among a behavior/cognition, emotion and social dimensions; contrary to Marin's initial account (Marin, 1991a).

Thus, the authors incorporated the social domain in the diagnostic criteria (Stuss et al., 2000). Third, apathy should cause identifiable functional impairments. Finally, apathy should not be fully explained by other factors, such as effects of a substance or major changes in the patient's environment. Interestingly, the experts decided to change the term "domain" for "dimensions" because of the known interactions between behavior/cognition, emotion and social GDB-related processes. Also, the authors stress that their classification refers to the dimensions for which impairment can be observed at the clinical level, contrary to Levy and Dubois' neuroscientific model.

Actimetry

Noteworthy, the experts encourage the use of information and communication technologies to provide objective measures of apathy. They deem actimeters sensors as providing objective assessment of apathy, recording the spontaneous activity of individuals in their environment (König et al., 2014; P. Robert et al., 2018). Actimeters are accelerometers which measure acceleration of the movement in three spatial dimensions (**Figure 1**). This device, typically worn on the wrist, is small, non-invasive, and easily worn by patients. Actimetry is thus a promising paraclinical tool for assessing apathy due to its objectivity in ecological setting and its user-friendliness.

Researchers have employed dimensional reduction techniques such as functional Principal Component Analysis (PCA) to identify associations between motor activity patterns and clinical dimensions of psychiatric disorders in the elderly, such as in apathy. Zeitzer and colleagues observed significantly reduced physical activity in Alzheimer's patients with apathy, unrelated to depressive disorders (Zeitzer et al., 2013) as well as a significant phase advance with earlier waking and sleeping times in apathetic subjects, corresponding to early-chronotype. The same patterns of motor activity, revealed by functional PCA, have also been correlated with social dimension of behavior such as working days (Difrancesco et al., 2021), poor global health (Difrancesco et al., 2021; Xiao et al., 2022) and severe prognostic such as cognitive decline or mortality risk in elderly (Zeitzer et al., 2018).

In general population, increased anxiety and severity of depression symptoms are correlated with reduced mean activity (Difrancesco et al., 2021) suggesting that physical activity could be an indirect indicator of depressive symptom severity. In depression, two meta-analyses robustly found that reduced mean activity was associated with days of depressive episodes but restituted after treatment intervention (Burton et al., 2013; Tazawa et al., 2019). In complex depression, such as bipolar disorders, PCA of motor activity corresponding to late-chronotype were also more present in depressive days and associated with a higher risk of depression relapse (Gershon et al., 2016). Hence, PCA of motor activity as measured by actimetry measure directly the relationship between circadian rhythm and psychiatric symptoms, and reproduced the association between late chronotype and psychiatric disorders found in the literature (Kivelä et al., 2018). Self-reported late-chronotype has been associated with pejorative course of depression such as elevated depression severity, greater cognitive complaints (Coleman & Cain, 2019) and higher risks of recurrence (Chan et al., 2014).

Taken together, these results suggest that actimetry is an interesting tool to investigate impaired ecological activity, as a complementary tool with clinician evaluation for monitoring ambulatory apathy in depression (König et al., 2014). However, the lack of specificity of actimetry to detect apathy requires precautions such as take into account comorbid conditions affecting patients' mobility and exploring carefully the psychiatric state of the patient.

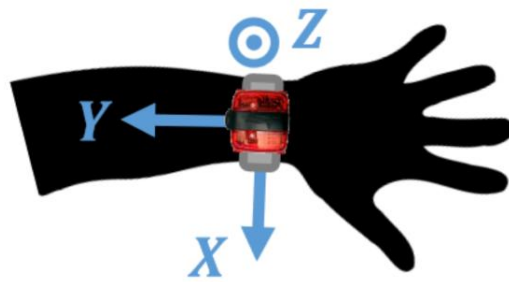


Figure 1. Example of a wrist actimeter
Acceleration of the wrist is recorded along the 3 dimensions.

2.3 The Goal-Directed Behavior Model

Taken together, current conceptions tend to conceive apathy as a dysfunction of processes underpinning goal-directed behaviors. The GDB model can be decompose in two dimensions: a cognitive and neuro-anatomical component.

Basic cognitive architecture

While many models of GDB exist, a synthesized framework has been proposed (Brown & Pluck, 2000). Following this model (**Figure 2**), purposeful behavior is first guided by an internal process or intention (1). This intention can be a conscious "desire," "wish," or "urge," which may stem from a preceding cognitive event, or it can be a relatively automatic response to an environmental stimulus. These internal states possess motivational qualities (2) which can either be innate or acquired through experience. These motivators alter the likelihood of a specific behavior being pursued and are often associated with emotional labels (3). For behavior to be classified as goal-directed, a prerequisite is that the individual must possess an internal representation of the goal (4), along with an understanding (conscious or unconscious) of a causal link (5) between a particular course of action and its outcome. The individual then constructs a suitable, sequentially organized action plan aimed at achieving the goal, which may involve evaluating it against alternative options and selecting the most appropriate one (6). Each of these sequentially ordered subtasks can be considered "intentional," even if they are not driven by a conscious "desire." This form of "intention to action" can occur in the absence of a primary prior intention, especially when the goal-directed behavior is triggered directly by an external event or is part of a repetitive or habitual task (7). In certain situations, individuals may need to exert cognitive action control (8), involving inhibition of habitual response tendencies that are inappropriate for the current context or managing other internal states that could interfere with the ongoing process. Initiating and executing the action or action sequence effectively (9) is, in part, influenced by the motivating properties associated with the goal (10), which dictate the level of intensity and effort invested. The control and maintenance of the activity rely on feedback from a comparator (11) that assesses the actual goal outcome against the internal goal representation. The output from this comparator either maintains or halts the ongoing action (12) and can also influence real-time adjustments to the action as the situation dictates (13).

In situations where the goal is distant, the action can be sustained through the motivating qualities of the goal representation (14). Achieving the goal is linked to a change in an individual's motivational state (15) and the associated emotional and hedonic responses (16). Attaining the goal and receiving a reward result in a positive response, strengthening the connection between the internal state and the

action taken to achieve the goal, thereby increasing the likelihood of choosing the same behavior in the future through a process of incentive learning. Conversely, failing to achieve the goal triggers a negative response, prompting consideration of alternative action plans, both immediately and in the future.

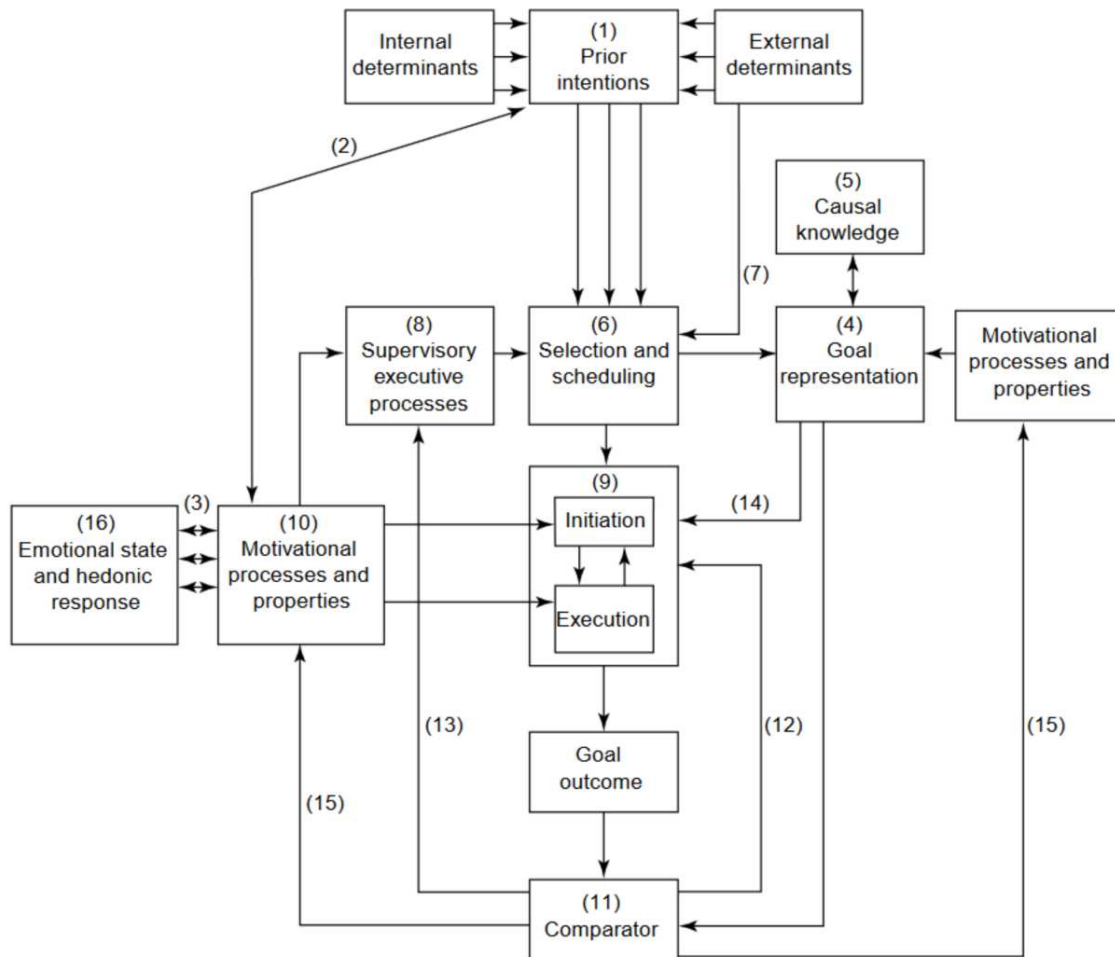


Figure 2. Basic Components of Goal-Directed Behavior Model (Brown & Pluck, 2000)

Neural implementation of the goal-directed behavior model

Hence, GDB-related cognitive processes are a coupling of value-based decision making, motivation, cognitive control and emotion processing. The GDB framework enables to directly relate GDB to the neural underpinnings of these well-studied cognitive processes (**Figure 3**).

For simplicity, the GDB model can be summarized into three processes (**Panels A, B and C, Figure 3**) (Le Heron et al., 2018; R. Levy & Dubois, 2006; Pessiglione et al., 2018): (i) a valuation system which computes the subjective value of the current and potential events, (ii) a mediating system which integrates this reinforcer or cost information to activate the motor system towards particular goals and (iii) a motor system which produces behavior towards motivationally relevant stimuli. Furthermore, behavior can be activated by flexible but effortful goal-directed systems, which actively represents the outcome of potential actions along with the costs of these actions, or by, simpler habitual systems, which activates responses based on previously learnt stimulus-response mappings. These motor control functions are hierarchically organized, such that complex behaviors are represented at higher level of abstract action as well as the lower level subcomponent behaviors (Duverne & Koehlin, 2017).

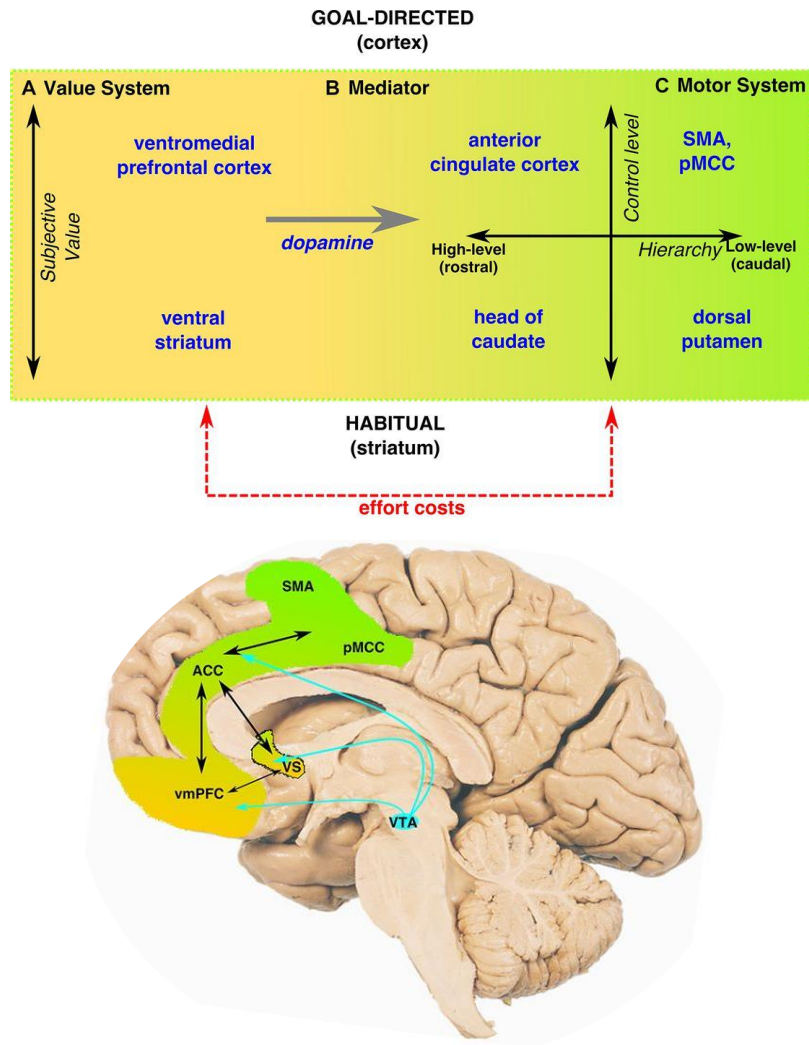


Figure 3. Brain Implementation of Goal-Directed Behavior (Le Heron et al., 2018)

The cognitive processes underlying GDB are instantiated neurally along a functional gradient from subjective valuation (in yellow) to motor execution (green).

ACC – anterior cingulate cortex; SMA – supplementary motor area; vmPFC – ventromedial prefrontal cortex; VTA – ventral tegmental area; VS – ventral striatum; VP – ventral pallidum

The value system includes the ventral striatum (VS), comprising the nucleus accumbens and adjacent areas in the rostral caudate nucleus and the ventral-rostral putamen, and the ventromedial prefrontal cortex (vmPFC), which includes the most rostral areas of the Anterior Cingulate Cortex (ACC) and adjacent areas of medial orbitofrontal cortex (OFC) (**Panel D, Figure 3**). The VS mediates learning which states of the environment predict future rewards (O’Doherty et al., 2004). The vmPFC is sensitive to the subjective value of events (Padoa-Schioppa, 2011) and for comparison across qualitatively different types of outcomes and reinforcers on a common scale (D. J. Levy & Glimcher, 2012).

Once computed, this value information is translated into an appropriate behavioral response via the mediating system. Both VS and ACC serve as crucial ‘limbic/motor’ interfaces, under the influence of the mesolimbic dopamine (DA), which originates from the ventral tegmental area of the midbrain and projects widely to these regions and related structures. The role of the mediating system plays a key role in integrating effort and rewards signals, computing the net value of performing an action (Pessiglione et al., 2018), as well as for option selection of the behavior (Klein-Flügge et al., 2016).

Finally, the production of behavior is mediated by the motor system, including posterior mid-cingulate cortex, supplementary motor area and dorsal striatum. This system is not a passive effective executor but interacts with more anterior regions, such as the motor cortex can facilitates the integration of a reward's subjective value with incentive-motivated performance (Galaro et al., 2019) and participates in cognitive control of action (Ridderinkhof et al., 2011).

Application to apathy

Apathy could stem from any dysfunction in one of these processes. Neuroimaging studies across various human neurodegenerative conditions have revealed that apathy is strongly associated with atrophy or functional disruption of the value and mediating systems notably the dorsal ACC (dACC), vmPFC, OFC and the VS (**Figure 4**). In patients with depression, a largely convergent network of brain regions showed blunted activation, relative to controls when performing tasks involving appetitive, cost–benefit decision and consummatory, or learning phases of reward processing (Gorka et al., 2014; Knutson et al., 2008; Pizzagalli et al., 2009) . Such activation concerns the VS, caudate, vmPFC or OFC and dACC, with substantial contradictory evidence between the studies (Husain & Roiser, 2018).

2.4 Conclusion

This brief background chapter has introduced key definitions and current conceptions of apathy, as a transdiagnostic entity encountered in psychiatric and neurologic conditions. A consensual model considers apathy as a dysfunction of cognitive processes underlying goal-directed behaviors. These processes involve prefrontal cortical regions encoding for valued decision making along an anteroposterior gradient from valuation system to effective realization of behavior, impaired in apathy. While clinical scales of apathy diverge in the construct their assess, due to their partial exploration of apathy, less theoretically-committed and more objective measures of ecological activity might help supporting a comprehensive study of apathy.

In the next chapter, we introduce apathy in late-life depression by exposing the clinical and scientific challenges this entity poses.

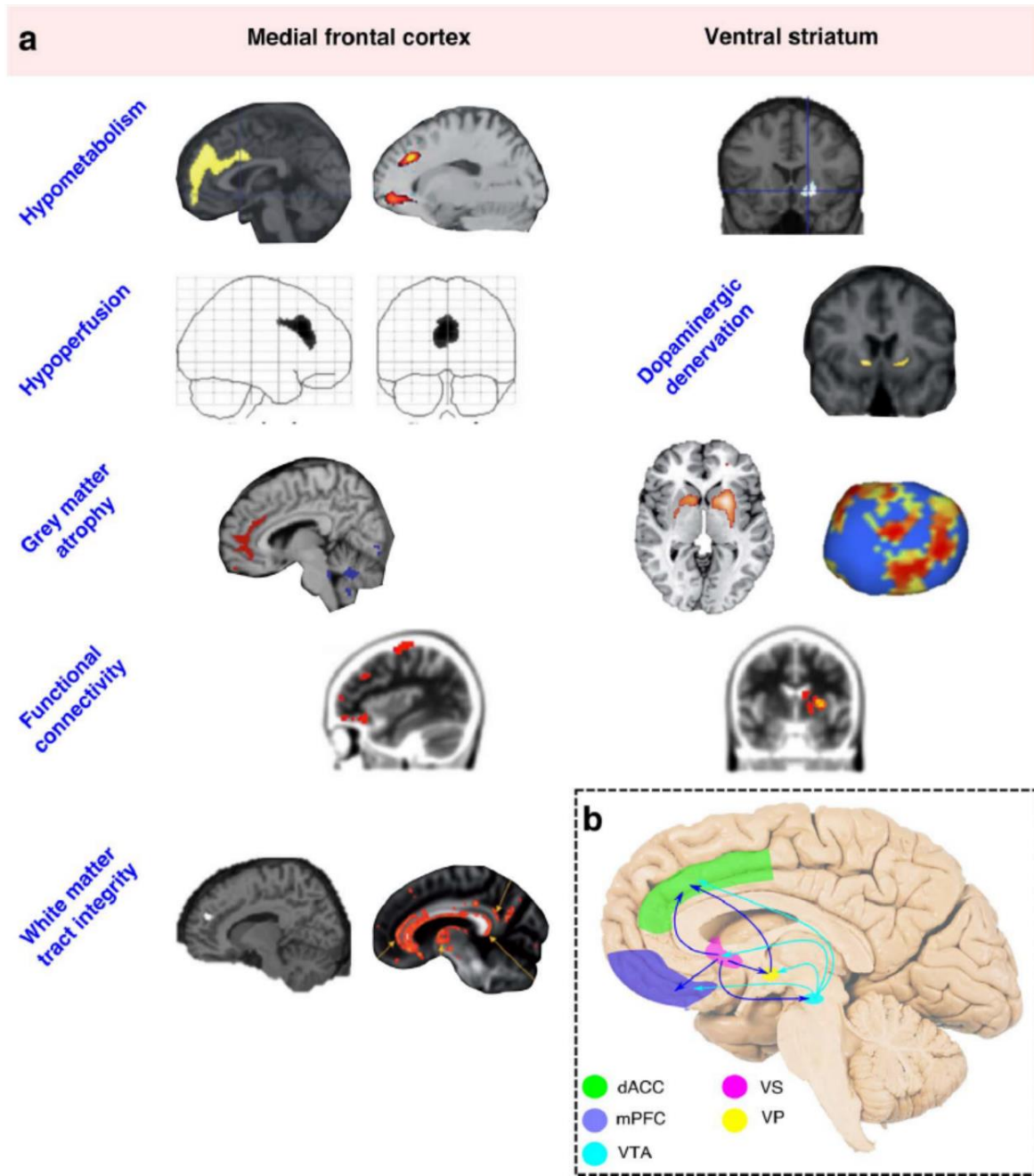


Figure 4. Consistent anatomical associations with apathy across imaging modalities and neurological disorders. (Le Heron et al., 2018)
dACC – dorsal anterior cingulate cortex; *mPFC* – medial prefrontal cortex; *VTA* – ventral tegmental area; *VS* – ventral striatum; *VP* – ventral pallidum

Chapter 3

Apathy in Late-Life Depression: Clinical and Scientific Challenges

OVERVIEW

Why studying apathy in late-life depression? This chapter reviews the current challenges for clinicians and researchers pertaining with apathy and late-life depression: the pejorative course associated with apathy in late-life depression, and the complexity of its pathophysiology.

3.1 Epidemiology of Apathy in Late-Life Depression

Late-life depression (LLD) is defined as the occurrence of a depressive episode in people age 65 or more. It is estimated that about 30% of the elderly population suffer from LLD worldwide (Horackova et al., 2019; Zenebe et al., 2021), representing 6 to 9% of the world population. LLD is a leading cause of disability in older adults and is associated with cognitive and physical decline, poor quality of life and excess mortality (Cai et al., 2020; Hall & Reynolds, 2014; Hölttä et al., 2012). Apathy concerns more than 30% of elderly with major depression (Chase, 2011; Forsell et al., 1993; Groeneweg-Koolhoven et al., 2016, 2017; Yuen et al., 2015) with a prevalence continuously increasing with age (M. Mehta et al., 2008).

Increased disability and risk factor of dementia

Apathy is associated with disability in everyday life by reduced personal life and social activities, even after taking into account depression severity (Hölttä et al., 2012; Yuen et al., 2015). This disability can be due in part by impaired executive dysfunction, found associated with apathetic LLD independently from depression severity (Feil et al., 2003; Funes et al., 2018; Lockwood et al., 2002). Results suggest that the cognitive deficits associated with apathy might extend to other cognitive functions such as slowed information processing (Butters et al., 2004), memory decline and global cognitive function, found correlated with sedentary, a direct consequence of apathy (Zaninotto et al., 2018). Moreover, meta-analyses estimated that apathy increased from 1.5 to 2 the risk of mild cognitive impairment (MCI) and incident dementia (Fresnais et al., 2022; van Dalen et al., 2018).

Persistent depression and poor treatment response

The presence of apathy is also associated with a higher likelihood of persistent symptoms. In a longitudinal cohort of LLD subjects, 80% of participants with apathy at baseline had persistent apathy and 50% had a persistent depression at 2 years, against 22% of persistent depression in the non-apathetic group at baseline (Groeneweg-Koolhoven et al., 2016). Poor response of apathy symptoms to antidepressant treatment in LLD have been robustly reported, despite of the possible amelioration of depression symptoms (Groeneweg-Koolhoven et al., 2016; Oberlin, Victoria, et al., 2022; Wongpakaran et al., 2007; Yuen et al., 2015). Reduced response to psychotherapies also involves apathy (Solomonov et al., 2021), the latter being correlated with reduced resilience in older population (Laird, Krause, et al., 2019), notably in LLD (Laird, Lavretsky, et al., 2019). Noteworthy, Solomonov and colleagues (2021) used a machine learning technique to order variables by their importance in predicting non-response to psychotherapies. Among the top ten predictors, five of them pertained to social

functioning such as perceived social support or participation and society, in addition to scores at the Apathy Evaluation Scale (AES). This advocates for the clinical utility to take social functioning into consideration in apathy in LLD.

3.2 Pathophysiological Models of Apathy in Late-Life Depression

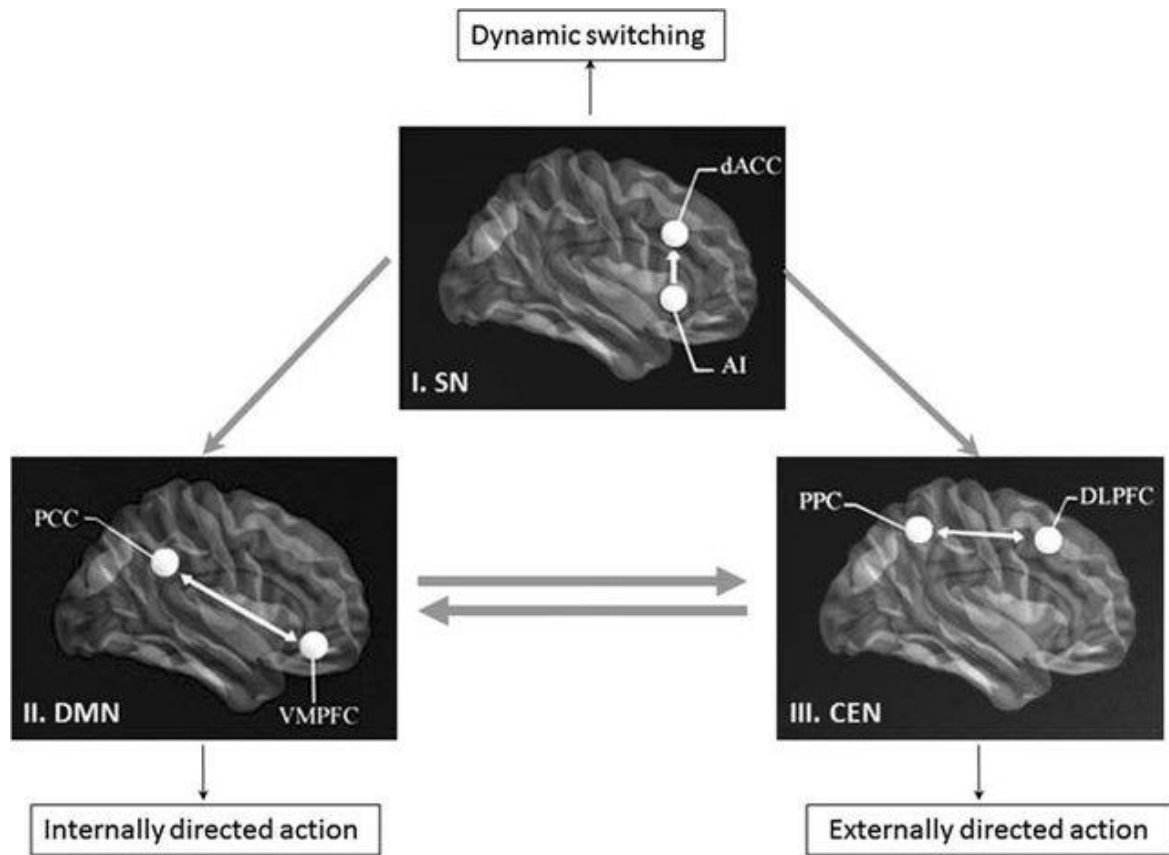
The clinical observations and conceptual knowledge on apathy in LLD have led psychiatrists to make hypotheses on the pathophysiological models in LLD explaining this syndrome. In this part, we cover three hypotheses formulated in apathy in LLD: the triple network hypothesis (Menon, 2011), the vascular depression hypothesis (Alexopoulos et al., 1997), the neuroinflammation hypothesis (Alexopoulos & Morimoto, 2011; W. D. Taylor et al., 2022). This section is largely inspired by the review of Alexopoulos (2019).

The triple network hypothesis

Menon (2011) proposed a triple network model composed of the executive control network (ECN), the default mode network (DMN), and the salience network (**Figure 5**). The executive control network, also named frontoparietal network, is composed of lateral prefrontal and posterior parietal regions activated in a wide variety of cognitively demanding tasks, principally associated with executive function or attention. In contrast, the default mode network is implicated in internally directed tasks such as self-referential mental processing, while being involved social cognitive processing or value-based decision-making, navigation, and autobiographical memory. Its core nodes are in the posterior cingulate cortex and the medial prefrontal cortex, with other nodes in the medial temporal lobe and the bilateral angular gyrus. Finally, the salience network consists of the bilateral anterior insula and the dorsal anterior cingulate cortex. These brain regions play an important role in attentional capture of biologically and cognitively relevant events and in the subsequent engagement of frontoparietal systems for working memory and higher-order cognitive control (Seeley et al., 2007).

The triple network framework states that the salience network mediates the “switching” between the DMN (**Figure 5.II**) and CEN (**Figure 5.III**) to guide appropriate responses to salient stimuli. Salience signals are integrated in the anterior insular cortex of the SN, and then influence signals in the DMN and CEN. These regions support internally directed and externally directed cognition, respectively. In depression, several mechanisms have been hypothesized regarding these networks. It has been suggested that DMN dominance over the other networks was due to its increased resting-state activity and facilitated by automatic, biased information processing (Wang et al., 2016). Abnormal SN-mediated switching between the DMN and CEN was also incriminated in the formation of negative schema and mood-congruent negative bias, associated with failure to effectively activate the CEN and recruit emotion-regulation processes.

The few functional MRI studies on apathy in LLD took this model as hypothesis. These studies have been limited to seed-to-whole-brain analyses derived from 3 regions of interest (ROI) including the dACC, the anterior insula and the dorsolateral prefrontal cortex (DLPFC) (Oberlin, et al., 2022; Yuen et al., 2014) or the nucleus accumbens (Alexopoulos et al., 2013). Apathy has been associated with increased resting-state functional connectivity between the dACC, the anterior insula and orbital cortices but decreased rsFC with prefrontal lateral regions, as apathy severity increases (Alexopoulos et al., 2013). Apathy was also correlated with higher rsFC between the anterior insula and the right DLPFC, mid-cingulate and premotor cortices, and reduced rsFC with the bilateral parietal posterior regions (Oberlin et al., 2022; Yuen et al., 2014). This hyperconnectivity between the insula and the DLPFC has been associated with non-treatment response in apathetic LLD (Oberlin et al., 2022), while hypoconnectivity between the dACC and DLPFC has been correlated with poorer executive functions (Gandelman et al., 2019) and apathy during effortful emotion recognition



(G. Robert et al., 2021) in LLD. Taken together, these results suggest that apathy in LLD and its traits are underpinned by an altered intrinsic rsFC of the executive network as well as a dysconnectivity of the anterior insula to recruit goal-oriented cognitive and motor processes (Wang et al., 2016; Yuen et al., 2014). These findings corroborate earlier structural brain imaging studies reported reduced grey matter volume of the dorsal anterior cingulate cortex (dACC) associated with apathy severity in LLD (Lavretsky et al., 2007), as well as a reduced cortical thickness of the anterior insula predictive of persistent apathy (Pimontel et al., 2021). Similarly, a structural connectivity analysis found reduced quantitative anisotropy in the splenium, cingulum, and fronto-occipital fasciculus in apathetic LLD patients, compared to non-aphathetic (Oberlin, Victoria, et al., 2022). These structural insults raise the question of their cause in LLD.

The vascular depression hypothesis

The vascular depression hypothesis postulates that cerebrovascular disease predisposes, precipitates or perpetuates syndromes such as apathy in LLD. This hypothesis is based on the observation that many LLD subjects have cerebrovascular risk factors, and that comorbid cerebrovascular diseases share and explain the poor clinical outcome found in apathy.

One key aspect of the clinical characterization of vascular depression is the presence of cerebrovascular risk factors or cerebrovascular disease. These risk factors include conditions like elevated systolic blood pressure (de la Torre, 2012) which can lead to various vascular changes such as to vascular wall hypertrophy or increased intima media thickness, reducing response to antidepressants (Paranthaman et al., 2012). Persistence of depressive symptoms has been associated with small basal ganglia lesions and large cerebral cortical white-matter lesions, while worsening of depression severity was associated with subcortical white-matter lesions (Steffens et al., 2002). Another essential feature of vascular depression is the worsening of depression in individuals who already had early-onset depression before the onset

of their vascular disease. For instance, markers of progression of cerebral small vessel disease such as white matter hyperintensities (WMH), subcortical infarcts or cerebral microbleeds were associated with new depressive symptoms in community elders (van Sloten et al., 2016).

From a neuroimaging perspective, vascular depression is characterized by the presence of hyperintensities in subcortical gray matter, deep white matter, and periventricular areas (Krishnan et al., 1997). These changes predict future depressive symptoms (Reppermund et al., 2014). Depression has been related to more severe WMH in various brain regions including the cingulum, uncinate fasciculus, and superior longitudinal fasciculus (Sheline et al., 2008; W. D. Taylor et al., 2013), as well as the frontal and temporal lobes (O'Brien et al., 2006). Studies using diffusion tensor imaging have revealed reduced anisotropy in the DLPFC and the uncinate fasciculus among patients with LLD indicating disruption in the white matter connections between the frontal regions and limbic areas (Wen et al., 2014). Additionally, one study reported decreased resting-state functional connectivity in the subgenual anterior cingulate cortex (sgACC) and increased connectivity in the dorsomedial prefrontal and orbitofrontal cortices in LLD (Wu et al., 2011). This abnormal connectivity was correlated with a higher volume of WMH in the same regions. Furthermore, individuals with LLD who had a high burden of WMH showed greater activation in the sgACC when performing a facial expression affective-reactivity task, suggesting that ischemic changes in the white matter contributes to heightened limbic activity.

The overall mechanism is represented **Figure 6**. Alexopoulos (2019) proposed that the convergence of interacting factors contributes to the emergence of vascular depression. White matter abnormalities, impeding the connectivity of networks supporting affect and cognition, would be caused by the modification of the cerebral blood flow (CBF) observed in LLD (Abi Zeid Daou et al., 2018). The authors observed an antero-posterior gradient of CBF from low frontal CBF to high CBF in the parietal lobe, temporal lobe, thalamus, and hippocampus. Lower CBF in the frontal lobe would explain apathetic symptomatology and dysexecutive function while high CBF in the hippocampus would participate to depress emotions.

The inflammation hypothesis

Another hypothesis relating LLD physiopathology to apathy involves inflammation. This model rests upon the evidence of immune dysregulation in the pathogenesis of depression in adults (Howren et al., 2009; Maes et al., 1997) and chronic low-grade inflammation in aging (Franceschi et al., 2000).

One argument for involving inflammation in LLD apathy stems from the common symptomatology and comorbidities associated with inflammatory markers. In older adults, epidemiologic studies robustly found association between depression severity and high levels of interleukin (IL) 6 (Bremmer et al., 2008; Dentino et al., 1999; Milanese et al., 2009; Penninx et al., 2003; Tiemeier et al., 2003), and to a lesser extent with IL-1 β levels in LLD (Thomas et al., 2005). Another study in LLD found a correlation between cognitive symptoms and plasmatic concentrations of the two inflammatory markers (Gimeno et al., 2009). Cognitive impairment, disability and mortality in late-life were also associated with increased plasmatic IL-6 (Ferrucci et al., 1999; Harris et al., 1999; Maggio et al., 2006; Roubenoff et al., 2003; Weaver et al., 2002; Wright et al., 2006). Finally, cardiovascular diseases have been correlated with serum levels of IL-6 (IL6R Genetics Consortium Emerging Risk Factors Collaboration et al., 2012), corroborating the vascular depression hypothesis.

This increase in inflammation is believed to affect multiple brain systems in the brain, associated with decreased hippocampal volumes (Satizabal et al., 2012) and WMH in the DLPFC (Thomas et al., 2000, 2002) in non-demented older adults. In adult depression, C-reactive protein and IL-6 levels moderated

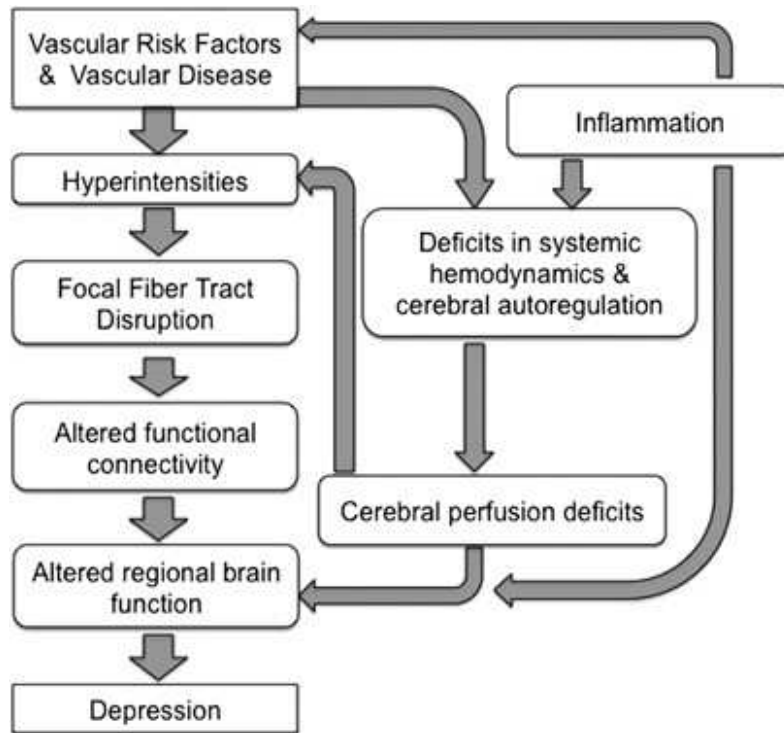


Figure 6. Mechanism of the vascular depression hypothesis (Taylor et al., 2013)

the association between anhedonia severity and reduced functional connectivity of the ventral striatum with the ventromedial prefrontal cortex (vmPFC), as well as the association between psychomotor slowing and decreased connectivity between dorsal striatum and vmPFC (Felger et al., 2016). Other studies reported a similar moderation effect of CRP on the association between depression and functional connectivity of regions related to the default-mode network (DMN) such as the vmPFC, the hippocampus, precuneus (Kitzbichler et al., 2021) and the amygdala (N. D. Mehta et al., 2018). One study in depression found a resting-state functional connectivity network associated with CRP comprising regions from the DMN with the vmPFC as a hub, whose connectivity was correlated with anhedonia symptoms (Yin et al., 2019).

From this literature, Taylor and colleagues (2022) proposed to understand the clinical presentation in LLD as a dysfunction of the dopamine system induced by neuroinflammation (**Figure 7**). The authors postulate that, in LLD, “*dopamine system dysfunction contributes to alterations in cognitive, positive valence, and/or sensorimotor systems that combine and interact, leading to cognitive difficulties, behavioral deactivation and frank depressive symptoms.*” Their model posits that increases in pro-inflammatory cytokines commonly observed in aging and depression has a detrimental impact on various aspects of dopamine system function. Consequently, this decline in dopamine system signaling would play a role in impairing cognitive function, positive emotional responses, and sensorimotor systems. Deficits sensorimotor systems in LLD refer to behavioral slowing, contributing to the seclusion and decreased activity in LLD patients. Gait slowing may also be a physical manifestation of slowed processing speed, with both measures increasing mortality risk in older adults (Sanders et al., 2017). In the beginning of the disease, symptoms in any of these systems may dominate and can be exacerbated by other risk factors related to an individual's genetic, medical, or social background. Moreover, deficits in a specific system may influence cognitive or behavioral symptoms mediated by other dopaminergic system, contributing to worsened depressive symptoms. For instance, cognitive control can be affected by motivational deficits (Botvinick & Braver, 2015) and is often accompanied by gait impairment (Camicioli et al., 2007), while motor cortex activity facilitate the integration of a reward's subjective value with incentive-motivated performance (Galaro et al., 2019). The authors

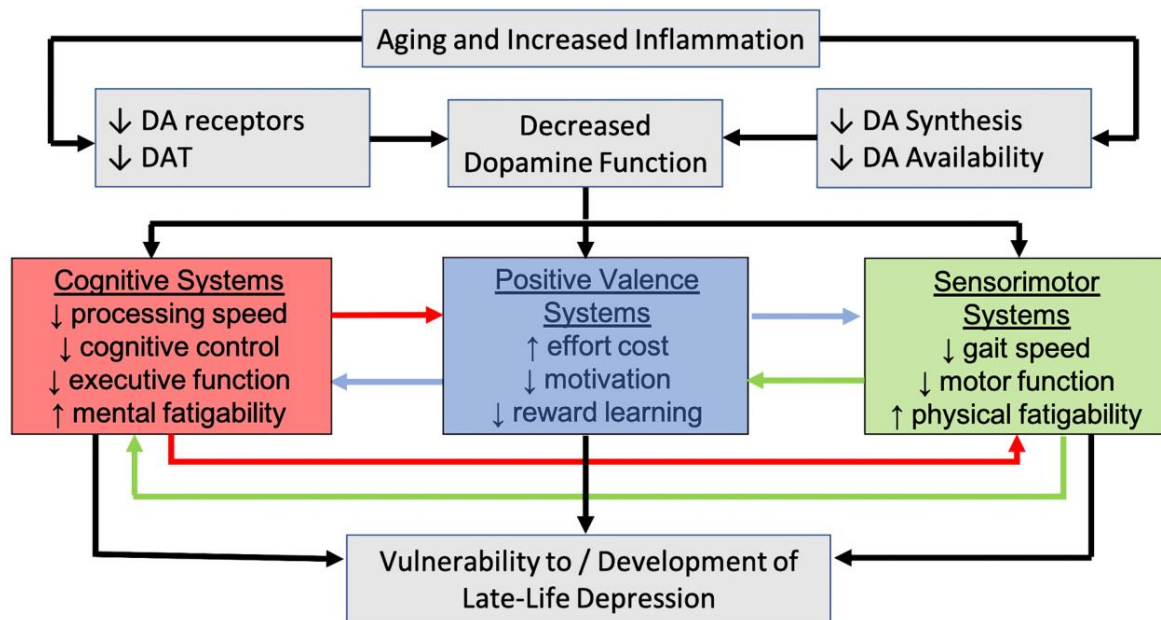


Figure 7. Model of dopaminergic system dysfunction in late-life depression (Taylor et al., 2022)

hypothesize that slowed processing speed and impaired cognitive control may increase the effort cost to achieve a goal, which in turn increases fatigability and the level of motivation needed to work towards goals. Poorer motor function may have a bidirectional relationship with fatigability, requiring even greater effort for any task and thus favoring inaction. Taken together, behavioral deactivation and reduced physical activity might be the results of individual contributions of these deficits in LLD.

To sum up, we presented three complementary pathophysiological models of apathy in LLD. The tripartite network hypothesis proposed that apathy in LLD is associated with deficit of recruitment of goal-oriented processes by the insula. The vascular hypothesis explains the anomalous perfusion of brain tissues, resulting in an imbalance of hypoperfusion of frontal regions and hyperperfusion of limbic regions which in turn yields white-matter lesions. The neuroinflammatory hypothesis postulates a low-grade cerebral inflammation which impairs dopamine synthesis or transport and, consequently, impact coupled systems involved in goal-directed behaviors: cognition, positive valence systems and sensorimotor systems. Taken together, a gap seems to exist between the richness biological hypotheses of apathy in LLD and mechanisms implied in goal-directed behavior on one side, compared to the characterization of its neural dysfunctions. We would like to finish this chapter by discussing some limitations of the studies interested in brain functional connectivity in apathy in LLD and by proposing possible solutions.

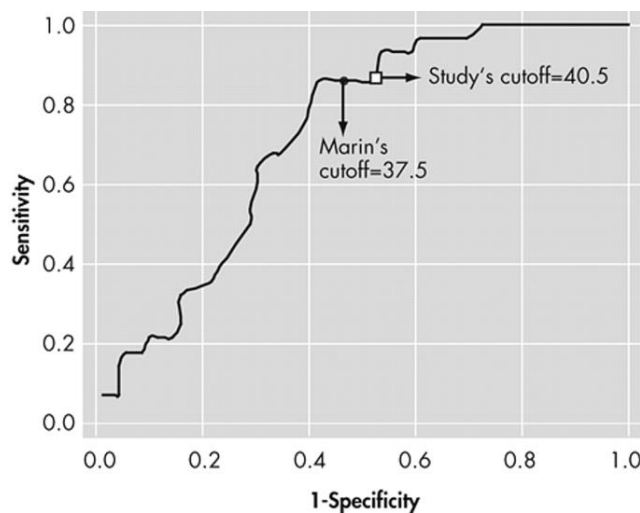
3.3 Methodological Considerations of MRI Studies

To our knowledge, only three fMRI studies have been interested apathy in LLD (Oberlin et al., 2022; Yuen et al., 2014; Alexopoulos et al., 2013), with one (Yuen et al., 2014) being a reanalysis of the other (Alexopoulos et al., 2013). Results of these studies are reviewed in **section 3.2**. All these studies rely on similar methods regarding evaluation of apathy and measurement of brain connectivity.

Thresholding of the Apathy Evaluation Scale

All three studies use the AES score and binarize it to classify patients in apathy or non-apaty group, using a threshold of 36.5. The authors justify the use of this threshold from a study which evaluates the psychometrics propriety of AES in dementia and reported a sensitivity of 88% for classifying apathetic patients at this value, but with a specificity of 50% (Clarke et al., 2007) (**Figure 8**). Hence, the previous studies present a significant risk of false positive, by misclassifying non-apaty patients in the apathetic group.

Another issue with the discretization of apathy in two classes is that it reduces the sample size of each group, reducing the statistical power of the analysis. With 16 LLD participants in two studies (Yuen et al., 2014; Alexopoulos et al., 2013) and 40 in one study (Oberlin et al., 2022), binarizing could at best estimate between-group differences based on a mean apathy score from 20 participants. On the other hand, considering the AES as a continuous variable would rely on a more validated usage of this scale and would take individual scores of all patients into consideration.



Exclusive usage of the Apathy Evaluation Scale

Figure 8. Receiving Operator Curve Analysis of the AES-Clinician Version (Clarke et al., 2007)

By exclusively using the AES, these studies do not provide a comprehensive evaluation of apathy. As reviewed in **Chapter 2**, social dimension and self-awareness (Ang et al., 2017; Sockeel et al., 2006) are considered important dimensions of apathy related to social interactions, not captured by the emotional dimension of the AES (Dickson & Husain, 2022). At the same time, the AES scores alone do not align with current 2018 diagnostic criteria for apathy by not taking into account social apathy and the functional impairment caused by apathy (Robert et al., 2018).

FMRI seed-based analysis

Seed-to-whole-brain analyses can be justified to identify intra and internetwork connectivity from connectivity of the key nodes implied in the tripartite network hypothesis (Menon, 2011). However, the definition of the seed is of importance. In studies of apathy in LLD, the definition of the seed varied in terms of technique and validity, from its identification on an anatomical atlas (Alexopoulos et al., 2013),

a set of voxels contained in a 8-mm sphere centered on the coordinates of the peak of a cluster in a previous study in 18 young adults (Yuen et al., 2014) and finally from a selected region of the Human Connectome Project–derived Glasser Parcellation Atlas (Glasser et al., 2016; Oberlin, Victoria, et al., 2022). By doing so, connectivity results from these studies might lack of robustness as well as of specificity on the activity on the actual region measured (Marrelec & Fransson, 2011; Noble et al., 2017) in comparison with resting-state networks studies.

3.4 Conclusion

Apathy is a frequent syndrome in LLD, difficult to treat, associated with a significant risk of persistent depression, cognitive decline and mortality. Although few studies have investigated its brain correlates in LLD, brain imaging studies tend to converge on finding abnormal connectivity of regions implied in goal-directed behaviors, notably in motivation and executive functions, in apathy across neurological diseases. Three complementary pathophysiological models proposed to explain these abnormalities: a neurofunctional account of default of switching of salience networks, a neurovascular model related to the tissue lesions, and a neuroinflammatory model explaining dopamine depletion. We observed a lack of brain imaging evidence characterizing apathy behaviors and dysconnectivity in LLD in the literature, compared to the current scientific interest on goal-directed behaviors. Comprehensive analysis of brain activity and multimodal evaluation of apathy combining different clinical scales and recordings of motor activity may provide deeper understanding of this disorder.

Part III

Materials and Methods

Chapter 4

Aims and Hypotheses of the Thesis

OVERVIEW

Can apathy in late-life depression be characterized as a deficit of goal-directed behaviors? This brief chapter presents the aims and hypotheses of the thesis and summarizes the approach undertaken.

4.1 Aim of the thesis

In the previous chapters, we covered the complexity of apathy assessments and theories, as well as the complexity of pathophysiological models of LLD. While current apathy models tend to converge towards insights of processes underlying goal-directed behaviors, the variety of apathy scales which exists explore differently apathy dimensions (Dickinson & Roiser, 2022). Recordings of motor activity could help to provide an objective measure of apathy in patients' ecological environment by comprehensively assessing a wide range of behaviors from different nature without suffering from the theoretical implications from psychological theories. However, by its lack of specificity, these tools should be used in combination with apathy scales. Regarding the complexity of pathophysiological mechanisms, the exploration of the neural underpinning of apathy in LLD is still poor and not related to the goal-directed behavior models, in comparison to what has been done in neurodegenerative diseases. A more thorough exploration of brain networks in their entirety in LLD, as well as the association between their activity, complementary apathy scales and motor activity might help to better understand apathy in LLD and promote the usefulness of actimetry in psychiatry practice.

The objective of this thesis was to evaluate whether daily ambulatory patterns of motor activity, related to apathy severity or diagnosis, were associated with functional perturbations of resting-state networks involved in goal-directed behaviors and with lesions of the related white matter fibers in LLD. To fulfill this goal, a transversal multicentric study was conducted in the hospitals of Rennes and Tours, to measure apathy, motor activity and brain structural as well as functional connectivity in depressed older-adults. The whole project can be decomposed into two studies.

Study 1

The purpose of study 1 was to assess the common and distinct perturbations in resting-state functional connectivity (rsFC) across clinical apathy measures and resting-state networks. Our primary aim was to characterize how intranetwork rsFC of networks involved in goal-directed behaviors was modified with respect to clinical apathy measures. We used three validated measures of apathy in LLD: the AES, the AMI and the 2018 diagnostic criteria for apathy. We also estimated the association between apathy and internetwork rsFC in a subset of medial prefrontal brain regions belonging to different networks, in order to reproduce the model of goal-directed behaviors (Le Heron et al., 2018).

Study 2

Study 2 answers more directly to the general objective of the thesis.

The aims of study 2 were (1) to determine if principal components of motor activity were associated with apathy severity and diagnosis, and (2) to characterize the modifications of intranetwork rsFC associated with principal components of motor activity related to apathy in networks underlying goal-

directed behaviors. We also aimed to localize the lesions along white matter tracts associated with principal components of motor activity related to apathy.

4.2 Hypotheses

Study 1

We hypothesized that using three apathy measurements would reduce the bias due to the measurement error of each individual instrument and help providing a more comprehensive view of the modification of rsFC associated with apathy. Overall, patterns of functional connectivity common to the 3 apathy measurements should yield consistent evidence of the cerebral basis of the cognitive, behavioral, social and emotional components of apathy. Following previous studies, we anticipated a decrease in rsFC within the default mode and cingulo-opercular networks (Oberlin et al., 2022; Yuen et al., 2014), and an increase in rsFC within the frontoparietal network (Alexopoulos et al., 2013; Oberlin et al., 2022) with apathy severity. Regarding the goal-directed behavior networks we defined, we expected a decrease in internetwork rsFC between the medial prefrontal regions.

Study 2

We expected that principal component scores of motor activity from the two top components would be associated with higher apathy scores, as reported in apathy in Alzheimer's disease. We also hypothesized that principal components of motor activity in LLD related to apathy will be associated with altered rsFC in the resting-state networks underlying goal-directed behaviors, as well as with a reduced fractional anisotropy and orientation dispersion index, but increased mean diffusivity and free water of white-matter tracts.

4.3 Conclusion

We exposed the aims of the thesis to (i) relate different apathy measures to functional brain connectivity, (ii) evaluate the relationship between motor activity to apathy measures and (iii) to relate motor activity to resting-state functional and structural connectivity. To establish these relationships, methodological choices on the analysis of imaging and actimetric data had to be made. In the subsequent chapters, we present the protocol of the study conducted to respond to these aims: chapter 5 details the Materials, chapter 6 presents the processing of functional MRI, and chapter 7 details the processing of actimetric data.

Chapter 5

Materials

OVERVIEW

This chapter presents the design and materials of the cross-sectional, observational study detailing: the inclusion criteria, the clinical, neuropsychological and motor activity assessments, and the MRI acquisition protocol.

5.1 Participants

Forty LLD patients and 30 healthy controls were recruited from the French old-age psychiatry centers of Rennes (Centre Hospitalier Guillaume Régnier) and Tours (Centre Hospitalier Régional Universitaire de Tours) between October 2019 and April 2022. Inclusion and exclusion were assessed during a psychiatric interview by a trained old-age psychiatrist.

Inclusion criteria

Inclusion criteria for the LLD group were: an age > 60 years-old, the presence of a major depression episode assessed by DSM-5 criteria of major depressive disorder (American Psychiatric Association & American Psychiatric Association, 2013) and the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998).

Healthy Controls (HC) were recruited such that HC and LLD groups were similar in terms of age and education level as both are confounding factors on brain activity (Edde et al., 2021; Perry et al., 2017; Stumme et al., 2020; Tomasi & Volkow, 2011).

Non-inclusion criteria

Non-inclusion criteria comprised: DSM-5 criteria for major neurocognitive disorder and Mattis Dementia Rating Scale (DRS) < 125 (Mattis, 1988) ; cerebral diseases (stroke, Parkinson's disease, multiples sclerosis); inflammatory or mechanical disease that might alter motor activity (severe arthritis or spondylitis); severe sarcopenia defined as a walk test < 1m/second at the 10 meter walk-test; extrapyramidal symptoms assessed at the Unified Parkinson's Disease III (Goetz et al., 2008); anti-psychotic prescription; high suicidality defined as a Clinical Global Impression Suicide Scale > 4; legal protection, deprived of liberty; and MRI contraindication (such as pacemaker or metal implants).

Written informed consents were collected. The study was approved by the relevant institutional review board (ID-RCB 2018-AO2643-52, NCT03807167).

5.2 Procedure

The day of the inclusion, LLD participants had a clinical assessment with a psychiatric evaluation. After inclusion, each participant underwent a neuropsychological assessment. After inclusion, each participant had their motor activity recorded for 4 days using an actimeter. After the 4 days of recording, participants underwent brain MRI scans. The same week or the week after, a neuropsychological evaluation was performed. **Figure 9** summarizes the design.

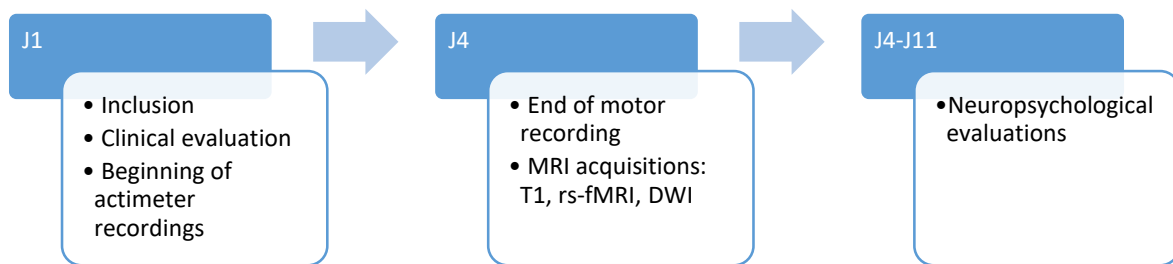


Figure 9. Design of the study

DWI – Diffusion Weighted Imaging; MRI – Magnetic Resonance Imaging; T1 – T1-weighted imaging protocol; rs-fMRI – Resting-state functional Magnetic Resonance Imaging

Clinical assessment

During the psychiatric interview, apathy was measured by the apathy diagnostic criteria of the 2018 international consensus group (Robert et al., 2018), the clinician-rated version of the AES (Marin et al., 1991) and the AMI (Ang et al., 2017). Depression severity was evaluated with the Montgomery-Åsberg Depression Scale (MADRS) (Montgomery & Åsberg, 1979).

Apathy Evaluation Scale – clinician rated version

The clinician-rated version of the Apathy Evaluation Scale is a semi-structured interview which evaluates apathy from the patient’s reported interests, activities and daily routine during the four last weeks. This scale consists of 18 items, each item being scored on a 4-point Likert scale. The items evaluate the cognitive, behavior or emotional dimension of apathy. The total score ranges from 18 to 72, with higher scores indicating more apathy.

Apathy Motivation Index

The Apathy Motivation Index is an 18-item self-report questionnaire which assesses apathy in terms of Behavioral Activation (tendency to self-initiate goal-directed behavior), Emotional Sensitivity (affective responses) and Social Motivation (level of engagement in social interactions). It uses a 5-point Likert scale with higher scores indicating more severe apathy.

The 2018 Diagnostic Criteria for Apathy

The Apathy Diagnostic Criteria of the 2018 international consensus group is a clinician-rated evaluation based on 4 criteria. First, a quantitative reduction of goal-directed activity in comparison to the patient’s previous level of functioning must be observed. Second, symptoms must persist for at least four weeks and affect at least two of the three apathy dimensions among a behavior/cognition, emotion or social dimension. Third, apathy should cause identifiable functional impairments. Finally, apathy should not be fully explained by other factors, such as effects of a substance or major changes in the patient’s environment.

Montgomery-Åsberg Depression Scale

The MADRS consists of 10 items (apparent sadness, expressed sadness, inner tension, insomnia, loss of appetite, difficulty concentrating, fatigue, loss of interest, pessimism, suicidal thoughts). Each of the items has six levels of severity, ranging from 0 to 6. Threshold scores for estimating depression severity are 7-19 for mild depression, 20-35 for moderate depression, and > 36 for severe depression (Thase et al., 2021).

Neuropsychological assessments

All participants underwent the same neuropsychological tests by trained neuropsychologists to evaluate executive functions. Planning and set-shifting were evaluated by the number of complete categories and preservative errors at the Modified Wisconsin Card Sorting Test (MCST) (Nelson, 1976). Speed processing and cognitive flexibility were measured with the Trail Making Test (TMT) A and B-A (Reitan, 1958). Cognitive control was evaluated from the interference score at the Stroop test (Golden, 1978). Semantic and phonemic verbal fluencies were also assessed (Cardebat et al., 1990).

Modified Wisconsin Card Sorting Test

The MCST is based on a card-sorting task. Cards are shown to participants who have to match them without explicit guidance. They receive feedback on the correctness of their matches. The test typically takes 12-20 minutes. The results yield the number and percentages of categories achieved, trials, errors, and perseverative errors. This test was developed to assess problem solving and the ability to shift cognitive strategies in response to changing environmental contingencies.

Trail Making Test A and B-A

The TMT evaluates speed processing and cognitive flexibility using two different visuomotor tracking conditions. In part A, the participant is required to connect circles with a pencil as quickly as possible in numerical sequence from the number 1 to 25. In part B, the participant is required to connect with a pencil 25 circles with letters and numbers disposed in a random order as quickly as possible, but alternating between numbers and letters and taking both series in ascending sequence. Cognitive flexibility is evaluated by subtracting the time needed to complete Part A from the time needed to complete Part B.

Stroop test

The Stroop test assesses the ability to inhibit cognitive interference, which occurs when the processing of an attribute of a stimulus interferes with the simultaneous processing of another feature of the same stimulus. Subjects were required to read three different tables as fast as possible. Two of them represented the “congruent condition” in which participants are required to read names of colors printed in black for one of them, and name different color patches for the other table. In a third table, named “incongruent condition”, participants have to read the color of the ink but with words printed in an inconsistent color ink. Time interference scores are calculated by subtracting a predicted score of the time needed to read words in the incongruent conditions in 45 seconds from the observed time of the participant.

Verbal fluencies

In the verbal fluency test, participants were asked to produce as many words as possible from a category in 60 seconds. We evaluated semantic category, including objects such as animals or fruits, and phonemic categories, including words beginning with a specified letter.

Actimeter recordings

Motor activity was recorded with actimeters models wGT3X-BT from the ActiGraph® company. Participants wore these devices on their non-dominant wrist and were instructed to keep them during four consecutive days to ensure 72 hours of recording (Littner et al., 2003; Sasaki et al., 2018). It is a practical and non-invasive medical device that minimally inconveniences the patient. The device was fixed on the wrist by a research assistant who recovered it the fourth day, just before the MRI acquisitions. To avoid intraindividual heterogeneity in motor activity related to change of habits between week days and week-ends (Heesch et al., 2018), recruitments were realized on Mondays or Tuesdays.

5.3 MRI acquisition

To reduce site variability between Rennes and Tours, all participants underwent MRI scans on 3T scanners of the same brand and model (Magnetom Siemens Prisma, VE11C, Erlangen, Germany) and 64-ch head coils.

Anatomic sequence

A whole brain T1-weighted MPRAGE image was acquired with repetition time (TR) = 1.9 sec, echo time (TE) = 2.26 msec, inversion time (TI) = 900ms, flip angle = 9°, 1 mm isotropic, field-of-view (FOV) = 256·256 mm², 176 slabs.

Resting-state fMRI sequence

During resting-state fMRI scanning, subjects were instructed to keep their eyes open, to remain still as much as possible, not think of anything, and not fall asleep. Transverse echo-planar imaging (EPI) images with opposite polarities of the phase encoding direction were acquired with the multiband accelerated EPI sequence Development Release R016a, from the Center for Magnetic Resonance Research, with the following parameters: TR= 1224 msec, TE= 30 msec, flip angle = 65°, multiband acceleration factor 3, in-plane resolution= 2.5 mm² isotropic, FOV = 210 · 210 mm², 54 axial slices with a thickness of 2.5 mm. A total of 288 volumes were collected in 6 minutes, plus 12 sec for the reversed phase.

Diffusion-weighted sequence

Diffusion weighted MRI were acquired by a 60-gradient multishell Cube and Sphere sequence (Scherrer & Warfield, 2012) with 1.5mm isotropic resolution, an acquisition matrix size of 148·148·90, 60 gradient orientations and 7 b₀ with an anterior-posterior phase encoding direction.

5.4 Conclusion

This chapter presented the design and materials of the observational study conducting in this thesis. Forty LLD patients and 26 healthy controls were recruited from the French old-age psychiatry centers of Rennes and Tours from October 2019 to April 2022. Inclusion and exclusion were assessed by a trained old-age psychiatrist. Inclusion criteria were patients ≥ 60 years old and DSM-5 criteria of major depressive disorder. Exclusion criteria were major cognitive disorders, neurological or arthropathic disorders, antipsychotic medication, high suicidal risk or MRI contraindications. At inclusion, LLD subjects had a psychiatric evaluation wherein apathy was evaluated by three valid and complementary evaluations of apathy. After the evaluation, participants were required to wear a wrist actimeter during 4 days. The last day of the wearing, participants underwent a resting-state functional and diffusion-weighted MRI scan.

Chapter 6

Methods: resting-state functional MRI processing

OVERVIEW

This chapter presents the preprocessing steps of resting-state functional MRI data and the statistical plan for intranetwork connectivity analysis. Overall, we performed a connectivity analysis based on regions-of-interest (ROI), or ROI-based analysis, on participants native spaces.

6.1 Preprocessing workflow

The aim of the preprocessing was to (i) correct for unwanted signals and (ii) to apply a brain parcellation atlas to the participant's native space.

Before the preprocessing, the first four volumes from each subject were directly discarded by the scanning machine to allow the signal to reach equilibrium and the participants to adapt to the scanning noise.

1 - Susceptibility distortion correction

Geometric distortions arise from variations in the magnetic properties of different tissues in the patient (such as skull and air boundary) which cause local field non-uniformity resulting in local image distortion. The acquisition of two EPI references with opposing phase-encoding directions enables the estimation of the displacement field from which a reconstruction of the undistorted image can be estimated via a least square method (Andersson et al., 2003). These algorithms are implemented in FMRIB software library (FSL) *topup* algorithm. The estimated fieldmap was then registered to the fMRI images and regularized by Gaussian smoothing, median filtering and despiking with FSL's *fugue*.

2 - Head motion correction and realignment

Head-motion parameters were estimated according to the median fMRI volume. FSL algorithm *mcflirt* registers each image from the whole BOLD time-series to the median image. This registration is performed by an estimation of the dissimilarity of the images via a normalized correlation cost function (Jenkinson et al., 2002). Sequentially, a search for the motion parameters is carried out from a coarse 8mm search, allowing the gross intensity patterns in the images to drive the registration, to 4mm searches with tighter tolerances. The cost-function is regularized by the introduction of geometric smoothing in order to avoid small discontinuities. This step enables the realignment of the volumes and the estimation of the parameters of the rigid body transformations needed (3 rotations and 3 translations).

3- Slice timing correction

MRI data is acquired in a sequential manner, often with a time delay between the acquisition of each slice. This can introduce temporal misalignment in the data, which can lead to artifacts in subsequent analyses. FSL's *slicetimer* helps to correct for these temporal misalignments by reordering the slices to match a specified reference time point. Slice timing correction is achieved using linear interpolation,

which estimates voxel values at non-acquisition time points. Interpolation weights are computed for each voxel, and a weighted average is taken from the two nearest time points to estimate voxel values at the desired time point. The output is a realigned dataset suitable for subsequent fMRI analyses, ensuring accurate temporal alignment of MRI slices.

4- Bandpass filtering

A bandpass filtering was applied to the BOLD signal to filter time series frequencies between 0.1 and 0.01 Hz. Bandpass filtering is multiple purposes such as noise reduction, notably physiological noise, it improves signal-to-noise ratio and remove low-frequency drifts unrelated with brain activity (Friston et al., 2000).

5- Registrations of brain atlas into native space

The median fMRI volume was co-registered to the participant's preprocessed structural image, using a rigid body transformation. Anatomical images were skull-stripped using an atlas-registration-based method, using the linear and non-linear block-matching algorithms (Commowick et al., 2012; Ourselin et al., 2000) available in the image processing toolbox Anima (<https://github.com/Inria-Visages/Anima-Public/wiki>).

The structural image was then registered to the Montreal Neurological Institute (MNI) template, using the linear and non-linear block-matching algorithms. For each subject, two image transformations were computed: the transformation from the mean functional volume to the structural volume and the transformation from the individual structural volume to the MNI template. By concatenating the above transformations sequentially, we obtained a direct transformation from each initial functional volume to the MNI space. The inverse of the transformation was applied to the Human Connectome Project-derived multimodal Glasser Parcellation Atlas (HCP) (Glasser et al., 2016) to register this atlas in the fMRI native space.

6- Nuisance regression

After these steps, nuisance regression was performed with 3 regressors. Residual motion was removed with the parameters estimated by FSL's *mcflirt*, computed by backwards differences (6 regressors). The physiological noise was reduced using regressors calculated by the CompCor method (Behzadi et al., 2007) implemented in nilearn (<http://nilearn.github.io/>). These 5 regressors correspond to the principal components from noisy regions-of-non-interest, such as white matter, cerebral spinal fluid and other non-brain signals.

Global signal was also included as a regressor by inspection of the connectivity matrix, to obtain a sparse connectivity matrix. Global signal regression is a popular technique which has several advantages such as removing prominent changes in signal intensities (Glasser et al., 2018), improving neuronal-hemodynamic correspondence (Keller et al., 2013) and strengthening association between functional connectivity and behavior (J. Li et al., 2019). However, global signal regression has been criticized to introduce negative correlations, so the signs of the resulting correlations might be hard to interpret (Murphy et al., 2009; Weissenbacher et al., 2009). Furthermore, because the global signal itself contains neuronal information and is associated with vigilance and arousal, some have argued against removing such information (Ben Simon et al., 2017; Glasser et al., 2018). A more unifying perspective suggests that analyses without global signal regression evaluates total fMRI fluctuation while analyses with global signal regression examines fMRI fluctuations relative to the global signal (J. Li et al., 2019; Yeo et al., 2015). Hence, global signal regression is a tool of choice for evaluating the elective effect of a variable like clinical scores or motor activity on brain signal.

Image quality control

Individual structural and functional images were inspected to remove subjects with significant artifacts or lesions. Participants were excluded if any of the following image quality metrics were above/below the specified threshold. Exclusion criteria were specified as an AFNI's mean quality index ("aqi") index > 0.025 , computed by the 3dTqual routine (Cox, 1996), a signal-to-noise ratio < 1 , a root-mean-square head motion above 2mm for translations and 1° for rotation, as accepted in elderly population (Doucet et al., 2021; J. R. Taylor et al., 2017).

For each volume, the aqi corresponds to one minus the Spearman's rank correlation of that volume with the median volume of a given subject. The aqi is a way to screen for sporadic abnormal images, such as the one caused by large subject head motion or scanner glitches. The signal-to-noise ratio was computed as the ratio between the mean signal of the fMRI time series and the standard deviation of the noise in the time series. The root-mean-square head motion displacements were calculated from *mcflirt* backward displacements.

With these criteria, 3 LLD subjects were excluded, two for significant artifacts and one for excessive head motion.

Brain parcellation

Cortical regions of interest (ROIs) were selected from the asymmetric HCP (Glasser et al., 2016). This reference cortical parcellation of the brain was derived from integration of multimodal magnetic resonance images and a semi-automated neuroanatomical approach (Glasser et al., 2016). Delineation and identification of cortical areas were performed by a machine-learning classifier from the integration of multimodal MRI images, before being interpreted by two neuro-anatomists. This atlas comprises 180 areas per hemisphere, which validity was assessed by robust differences in signal between neighbor regions.

We investigated the intra-network connectivity of the default mode (79 nodes), the cingulo-opercular (54 nodes), the somatomotor (38 nodes) and the fronto-parietal networks (44 nodes), following the Cole-Anticevic brain-network parcellation (Ji et al., 2019). The Cole-Anticevic parcellation was obtained by its developer by Louvain clustering to detect communities of networks for a range of gamma-values. The final cortical partition was a result of two criteria: a plausible number of networks that included primary sensory/motor networks had to be present, and the most stable and modular partition solution was chosen. The final parcellation retained twelve resting-state networks (RSN) (**Figure 10**). Noteworthy, this parcellation do not identify the salience network *per se* but a higher ordered one: the cingulo-opercular network, containing the salience network.

According to current models apathy as impaired goal-directed behaviors (Le Heron et al., 2018), we defined a subconnectome network of 38 nodes using the same parcellation by selecting the medial regions of all the networks and the orbito-affective network. We hypothesize that limiting the analysis of internetwork connectivity to the relevant ROIs implied in goal-oriented behavior would enable to identify the putative stages of the cognitive processes modified with apathy.

6.2 Statistical Methods

Correlation matrix

From the brain parcellation obtained, functional connectivity measures between every combination of pairs of ROIs were estimated using a Pearson's correlation. A Fisher's r-to-z transformation was applied to obtain a correlation matrix of normalized z-scored correlation coefficients.

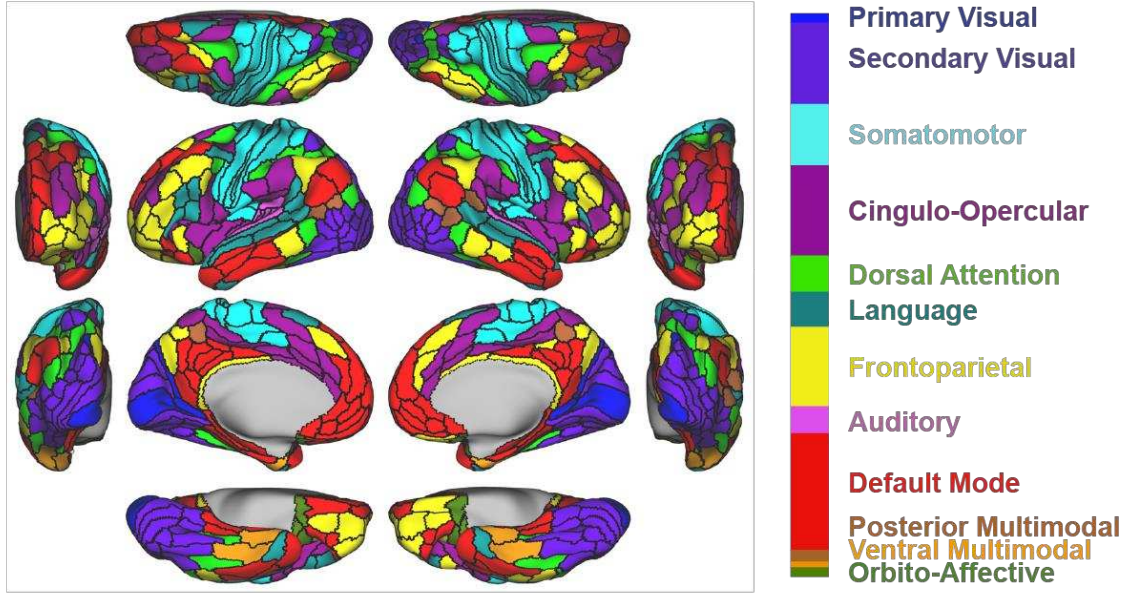


Figure 10. The Cole-Anticevic Brain Network Parcellation and corresponding resting-states networks (Ji et al., 2019)

Threshold-free network-based statistics

To identify the association of apathy on functional connectivity, we performed the threshold-free network-based statistics (TFNBS) (Baggio et al., 2018). This method combines the network-based statistics approach (Zalesky et al., 2010) and the threshold-free cluster enhancement algorithm for voxel-wise analysis (Smith & Nichols, 2009).

The network based-statistics (NBS) is a statistical method which aim to identify clusters of edges within a network while controlling for family-wise error rate. This method offers greater statistical power than traditional correction methods such as the false discovery rate correction (Zalesky et al., 2010). The steps of the NBS method are represented **Figure 11**.

The procedure begins by estimating the association between the z-scored correlation coefficients of each pair of ROIs and the variable of interest via a linear regression model:

$$C_{i,j} = \beta_0 + \beta_1 X_i + \sum_2^n \beta_k Z_{ki} + \varepsilon_{ij}$$

Where $C_{i,j}$ the correlation coefficient for subject i and a pair of ROIs j ; X_i is the independent variable of interest for subject i ; Z_{ki} is the k th covariate among n for subject i ; β_0 the intercept of the model; β_1 is the regression coefficient of the variable of interest; β_k the regression coefficient of the k th covariate; ε_{ij} represents the error term for subject i and pair of regions j . In this model, the residuals are independent and identically distributed. The covariance error matrix is a diagonal matrix $Var(\varepsilon_{ij}) = \sigma^2 \mathbf{I}$, with σ^2 the constant variance of the residuals and \mathbf{I} the identity matrix. However, connectivity between pairs of regions might be themselves more or less correlated within a same subject, which might contrary the supposed independence of residuals. One might prefer using linear mixed effect models which take into account this nested structure of data (*i.e.* brain regions within subjects). These

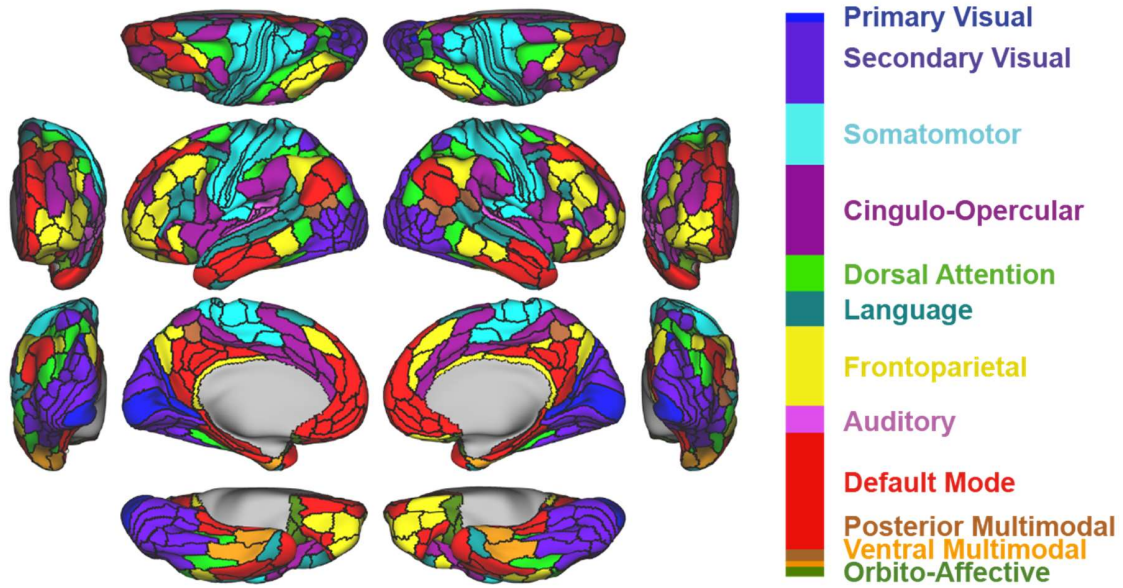


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models consider the subject as a multivariate normally distributed random variable of variance u_i between subjects (Pinheiro & Bates, 2009). The updated model becomes:

$$C_{i,j} = \beta_0 + \beta_1 X_i + \sum_2^n \beta_k Z_{ki} + u_i + \epsilon_{ij}$$

The new covariance error matrix $Var(\epsilon_{ij}) = \sigma^2 \mathbf{R}$ is the within-subject variability, with \mathbf{R} a block-diagonal matrix where each block corresponds to a subject or group. The blocks on the diagonal represent the covariance structure within each group. From the fixed-effect or the random-effect model, a triangular matrix of β_1 is constructed. Based on an *a priori* threshold chosen by the researcher, all edges with a coefficient superior to the threshold and sharing nodes in common are considered as a component. The sum of the β_1 inside the same component is the component height, and the number of nodes it contains is the component size.

Permutations are then performed a large number of times, using the same models, by shuffling randomly the values of the variable of interest X across subjects. The maximal height and maximal size of surviving components are then stored at each iteration to constitute a null-distribution of maximal component heights and a null-distribution of maximum component extent are obtained. This provides an empirical approximation of the null-distribution (Nichols & Hayasaka, 2003). Let H_0 denote the case where the null hypothesis is true for every connection, let s_i denote the strength or the extent of the connected graph component i and let α be the nominal family-wise error rate (FWER). By definition, it follows that:

$$\begin{aligned} FWER &= \mathbf{P}(\mathbf{1 \text{ or more components declared significant} } | H_0) \\ &= 1 - \mathbf{P}(\mathbf{no component declared significant} | H_0) \\ &= 1 - \mathbf{P}\left(\bigcup_i^n \{s_i \leq t_\alpha\} | H_0\right) \\ &= 1 - \mathbf{P}\left(\max_i \{s_i\} \leq t_\alpha | H_0\right) = \alpha \end{aligned}$$

Thus, storing the maximal strengths provides a direct estimation of the null-distribution

$F = \mathbf{P}\left(\max_i \{s_i\} \leq t_\alpha | H_0\right)$ where the component strength threshold, t_α , is determined for an α -level significance by $t_\alpha = F^{-1}(1 - \alpha)$.

One main drawback of the NBS technique is the setting of an arbitrary threshold for statistical significance. The TFNBS method (**Figure 12**) proposes to perform the same first methods – linear regression and component selection but with the following modifications:

1. A threshold is applied to the F-statistics matrix of regression coefficients, at a series of steps h , with a step interval defined as a hundredth of the maximum value of the matrix. The F-statistics is performed to estimate the statistical significance of the fixed effect of interest by a likelihood ratio test. This test calculates the maximized marginal likelihood of the model, using a Type III analysis of variance to test the null hypothesis that the fixed effect has no effect on the dependent variable. The F-statistics used to assess the ratio of the explained variation (SS_{effect}) to the unexplained variation (SS_{error}), adjusted for the degrees of freedom of the numerator (df_{effect}) and denominator (df_{error}):

$$F = \frac{SS_{effect} / df_{effect}}{SS_{error} / df_{error}}$$

We used the most conservative method, the Kenward-Roger approximation, to estimate the degrees of freedom.

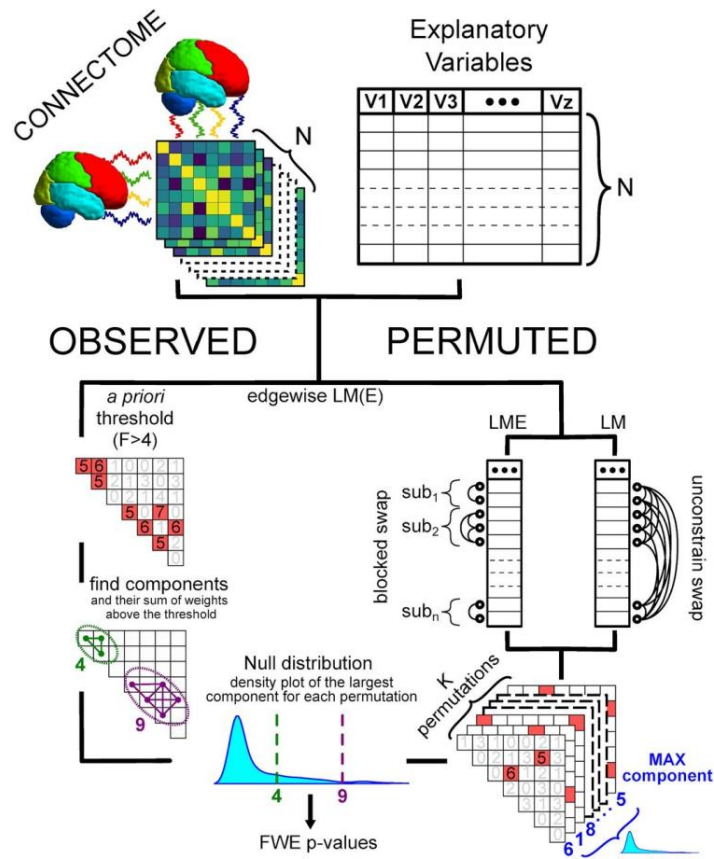


Figure 11. Network-based statistics diagram (Gracia-Tabuenca & Alcauter, 2020)

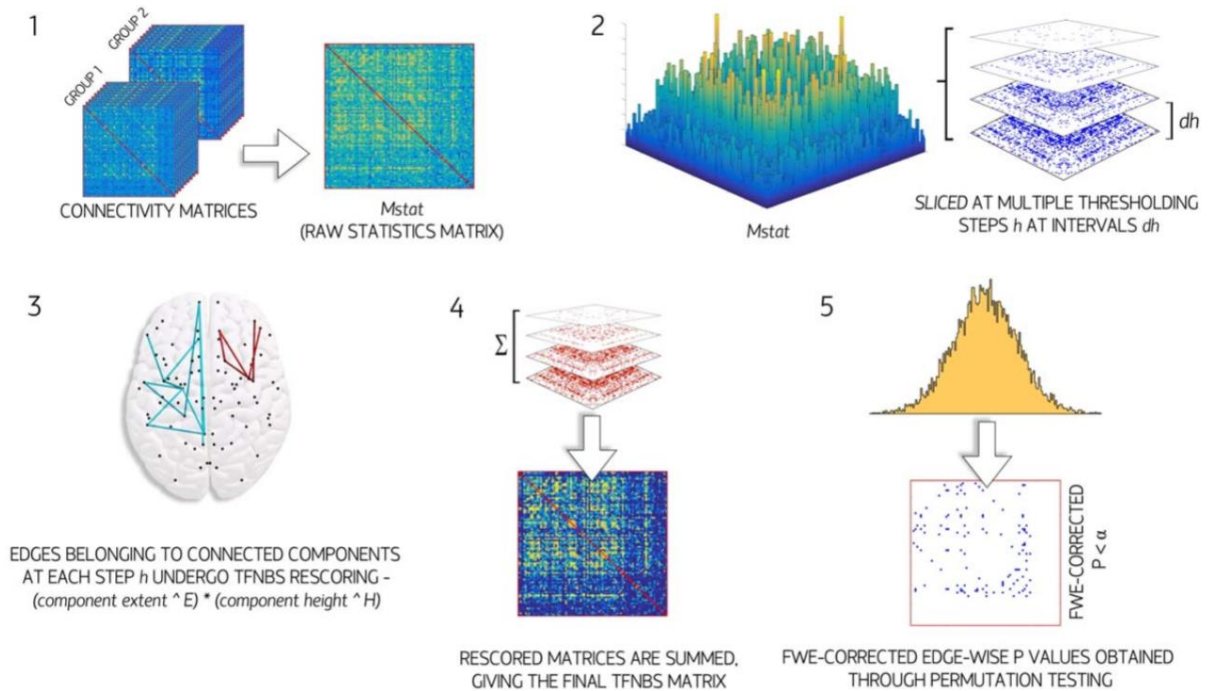


Figure 12. Threshold-Free Network-based statistics diagram (Baggio et al., 2018)

2. Then, at each thresholding step, the value of each matrix suprathreshold element belonging to a connected component is replaced by the component's size raised to the power E , multiplied by the component's height raised to the power H .
3. The matrices obtained at each step are subsequently summed giving the final TFNBS score for every network edge.
4. Statistical significance is then established through permutation testing to obtain a null-distribution.
5. This method enables to identify subnetworks of statistically associated with a with a variable.

In our study, we performed separately the TFNBS algorithm for each resting-state network to measure intranetwork resting-state functional connectivity. The association between the z-scored correlation coefficient of each pair of ROIs and the variable of interest (apathy group, AES score, AMI score or principal component of motor activity) was investigated by three distinct linear models, regressing out for age, gender, education and city site. As recommended in a similar population (Baggio et al., 2018), we set the E parameter value to 0.75 combined with a H parameter value of 3.25. Statistical significance was established through permutation testing over 10000 permutations.

Marginal Mean Effects

As the TFNBS method only enables an identification of the subnetwork by F-statistics but not the direction of the effect size, we calculated the marginal mean effect of the ROIs by network and measure as well as the concordant results across the three apathy measures. These estimates are conditional averages, corresponding to the expected differences in correlation for each ROI level for a one point difference in apathy score, holding other predictor variables constant, computed from the mixed model predictions. The estimation of the marginal mean effect was performed in two steps. First, a linear mixed model effect was used with the ROI-to-ROI correlation as the response, the interaction between the values of the apathy evaluations and the ROI as fixed effects of interests, adjusted on the age, the sex, the years of education, and with the subject as a random intercept. For each ROI, the marginal effect of the apathy measures on correlation was calculated via the `emmeans()` function of the `{emmeans}` package using R Statistical Software (v4.2.1; R Core Team 2022).

6.3 Conclusion

We detailed the preprocessing steps of MRI data for denoising and registration atlas from MNI-space to native space. The selection of the regions of interest were made from the HCP atlas, and we identify the corresponding resting-state networks according to the Cole-Anticevic atlas. We presented the network-based statistic approach, a non-parametric powerful statistical method, which enables to identify subnetworks whose connectivity is associated with a variable of interest. The main drawback of this method is the arbitrary choice of the statistical significance. We thus chose to use the threshold-free network-based statistic which calculates an adaptive threshold to correct for multiple comparison due to the number of nodes.

Chapter 7

Methods: Actimetry processing

OVERVIEW

This chapter details the method we performed for pre-processing actimetric data, estimating individual smoothed motor activity from the 3-day recordings by generalized additive models, and predicting the functional principal components of motor activity of individual participants.

7.1 Preprocessing of Actimetry Recordings

Data were collected using a wrist-worn activity monitor, which is used to record information on the physical activity, namely ActiGraph wGT3X-BT. Actigraph values were imported in the Actilife software.

The software displays counts, which are the result of summing post-filtered acceleration values around each axis (raw data sampled at 30 Hz) into epochs. The epoch length represents the amount of time over which raw acceleration data are summed after filtering.

First, raw counts over the recording period were inspected to ensure a minimum of 72h of recorded activity. The actigraph device detects non-worn period via a metallic plate on the back of the battery which detects monitor removal when worn against the skin. Subjects with missing values were excluded from actimetry analyses.

After verification of the raw data, data were converted in an epoch length of 30 seconds. Data between midnight and 5 a.m. were removed, due to the high rate of estimated missing values and because we were interested in diurnal activity related to apathy. Then, a file consisting of counts values over the three axes was generated for each participant and the vector magnitude of the counts on each axis was computed as:

$$\|a\| = \sqrt{a_x^2 + a_y^2 + a_z^2}$$

With $\|a\|$ being the vector magnitude and a_i the count activity along the i axis, $i \in \{X, Y, Z\}$.

Data were log-transformed before subsequent analysis.

7.2 Smoothing of Actimetric curves

As motor activity was recorded on three days, we wanted to provide an estimate of motor activity before principal component analysis. We used a generalized additive mixed model (Hastie & Tibshirani, 1986; Wood, 2017) to smooth the data and use their prediction for subsequent analysis. These models provide an estimate of the participants' traces over the 3-day recording period, considering the hierarchical structure of the data and temporal autocorrelation of the measurements.

Principle of generalized additive models

Generalized additive models (GAM) are extensions of linear regression models which allows the relationships between independent variables and the response to be described by smooth curves:

$$E(Y) = g^{-1} \left(\beta_0 + \sum_{j=1}^J f_j(x_j) \right)$$

Where $E(Y)$ is the expected value is the expected value of the response Y (for an appropriate distribution and link function g), f_j is a smooth function of the variable x_j , β_0 is an intercept term, and g^{-1} is the inverse link function.

Each smooth function f_j is represented as the sum of K simpler basis functions $b_{j,k}$ multiplied by corresponding coefficients $\beta_{j,k}$ which has to be estimated such that:

$$f_j = \sum_{k=1}^K \beta_{j,k} b_{j,k}(x_j)$$

K is the basis size, determining the maximum complexity of the smooth function.

As a large basis size could lead to overfitting, a smoothing penalty is added to prevent excess wiggleness and ensure appropriate complexity of each smooth function. For each smooth function, one or more penalty matrices S , specific to the basis functions, is pre- and post-multiplied by the parameter vector β to calculate the penalty ($\beta^T S \beta$). The penalty term is then subtracted from the model log-likelihood L , controlling the trade-off via a smoothing parameter λ . The penalized log-likelihood used to fit the model is:

$$L - \lambda \beta^T S \beta$$

The optimal smoothing parameter λ is estimated by restricted maximum likelihood, optimizing the wiggleness of the curve.

Different type of smooth functions can be used with their respective penalty matrices. For cyclic data, a cyclic cubic regression spline can be chosen. These smooth functions penalized the basis coefficients such as the start and end of the function match in values and in first derivative (Wood, 2001).

Generalized mixed additive models

As motor activity are nested in day, it is important to take into account intergroup variability. This can be realized in five different forms (**Figure 13**) (Pedersen et al., 2019):

- A single common smoothing function for all observations;
- A global smoothing function plus group-level smoothing functions that have the same wiggleness; corresponding to a global smoothing function with individual effects that have a shared penalty;
- A global smoothing function plus group-level smoothing function with differing wiggleness.
- Global smoothing function with individual effects that have individual penalties;
- Group-specific smoothing function without a global smoothing function, but with all smoothing function having the same wiggleness;
- Group-specific smoothing function with different wiggleness.

Concerning individual motor activity, we tested the 5 models (model G) serving as a reference. We chose a cyclic cubic regression spline as the basis for the fixed effect of time, constraining the activity% at the beginning and end of the day to have the same value and rate of change over time. For the random subject effect, we defined a factorial filtering base (determining a function and/or smoothing parameter for each subject).

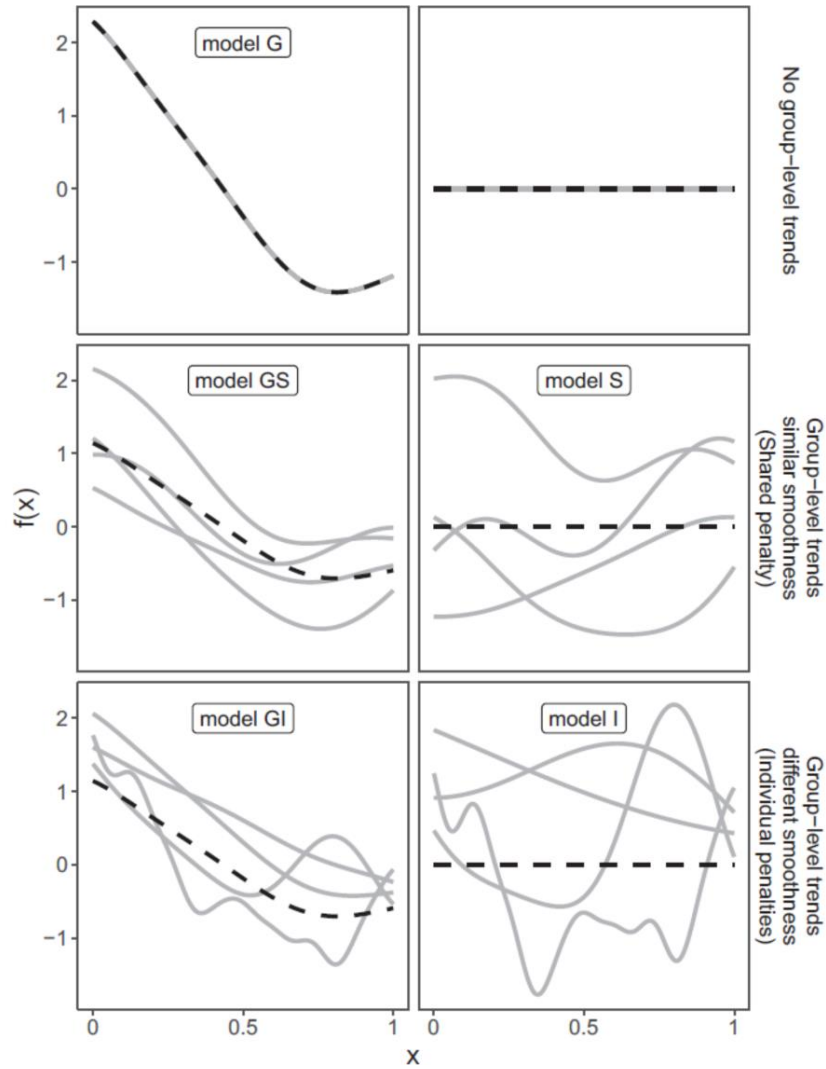


Figure 13. Alternative types of mixed GAM models (Pedersen et al., 2019)

The diagnosis of each model and selection of the optimal base size was assessed by the distribution of residuals using the `gam.check()` function (Wood, 2017). The best model was selected based on the minimal Akaike criterion (Wood et al., 2016) and minimal mean squared error leave-one-out cross validation score over the days (Pedersen et al., 2019). As the Akaike criterion penalized more complex models, we also visually inspected the prediction of the model with respect to raw count data to select the model.

7.3 Functional Principal Component Analysis

Eigen Decomposition

For functional principal component, we did a grid approximation of the method described in Ramsay & Silvermann (2005).

We store the individuals predicted smoothed activity in a $N \times T$ matrix \mathbf{X}^* , with N the number of subjects and T the number of data points in a day. Data were recentered around the origin by subtracting the

mean activity from \mathbf{X}^* , giving the matrix \mathbf{X} . Then, the covariance matrix $\mathbf{X}^T \mathbf{X}$ of dimension $T \times T$ was computed.

By singular value decomposition of the covariance matrix at each time point, p eigenvalues and p eigenfunctions of length T were calculated. Eigenfunctions and eigenvalues were scaled before computing the explained variance of each component, defined as the ratio of the scaled eigenvalue over the total sum of the scaled eigenvalues. We selected the top 4 components, explaining 85% of the variance.

Interpretation

The principal components provide a qualitative representation of interindividual variations in activity which can be summarized as one value. For representation purposes, we can add or subtract to the mean activity an amount of the eigenvalue projected on a specific eigenfunction. For instance, for a component i , we note its standardized eigenvalue ω_i and the standardized eigenfunction $\varphi_i(t)$. We can add or subtract to the mean centered activity the quantity $\delta(t)$:

$$\delta(t) = \sum_{t=1}^T 2 \times \sqrt{\omega_i} \times \varphi_i(t)$$

The quantity $\delta(t)$ is a projection of a certain amount of ω_i on the eigenfunction $\varphi_i(t)$, analog to one standard deviation of the deformations along the directions of $\varphi_i(t)$ for each time point.

Individual principal component scores for component i were calculated by multiplying for a subject n , his centered curve \mathbf{X}_n by ω_i and dividing over T . This quantity gives the weighted average of the individual variations of activity for a specific component.

Part IV

Clinical Studies

Chapter 8

Study 1

Connectivity patterns of the core resting-state networks associated with apathy in late-life depression.

OVERVIEW

The following study answers: what are the relationships between apathy and intranetwork resting-state connectivity? And how does intranetwork resting-state connectivity vary as a function of the apathy scales? We present the results of our study pertaining to apathy clinical scales and functional connectivity. This study found that 3 apathy measurements were associated with modified intra resting-state network connectivity in key networks implied in goal-directed behaviors. The apathy scale related to social apathy, the AMI, showed stronger associations with the cingulo-opercular and frontoparietal networks, whereas the AES had stronger associations with the default mode network and the goal-oriented behavior network. Our findings indicate that apathy in LLD is consistently associated with changes in both intranetwork resting-state connectivity and internetwork resting-state connectivity of brain regions implicated in goal-oriented behaviors with some specificities between the scales. This study has been published in *Journal of Psychiatry & Neurosciences* (Roy et al., 2023).

Connectivity patterns of the core resting-state networks associated with apathy in late-life depression

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Background: Apathy is associated with reduced antidepressant response and dementia in late-life depression (LLD). However, the functional cerebral basis of apathy is understudied in LLD. We investigated the functional connectivity of 5 resting-state networks (RSN) hypothesized to underlie apathy in LLD. **Methods:** Resting-state functional MRI data were collected from individuals with LLD who did not have dementia as well as healthy older adults between October 2019 and April 2022. Apathy was evaluated using the diagnostic criteria for apathy (DCA), the Apathy Evaluation Scale (AES) and the Apathy Motivation Index (AMI). Subnetworks whose connectivity was significantly associated with each apathy measure were identified via the threshold-free network-based statistics. Regions that were consistently associated with apathy across the measures were reported as robust findings. **Results:** Our sample included 39 individuals with LLD who did not have dementia and 26 healthy older adults. Compared with healthy controls, individuals with LLD had an altered intra-RSN and inter-RSN connectivity in the default mode, the cingulo-opercular and the frontoparietal networks. All 3 apathy measurements showed associations with modified intra-RSN connectivity in these networks, except for the DCA in the cingulo-opercular network. The AMI scores showed stronger associations with the cingulo-opercular and frontoparietal networks, whereas the AES had stronger associations with the default mode network and the goal-oriented behaviour network. **Limitations:** The study was limited by the small number of participants without apathy according to the DCA, which may have reduced the statistical power of between-group comparisons. Additionally, the reliance on specific apathy measures may have influenced the observed overlap in brain regions. **Conclusion:** Our findings indicate that apathy in LLD is consistently associated with changes in both intra-RSN and inter-RSN connectivity of brain regions implicated in goal-oriented behaviours. These results corroborate previous findings of altered functional RSN connectivity in severe LLD.

Introduction

Apathy is a prominent and persistent syndrome in late-life depression (LLD) associated with poor functional outcomes¹ such as reduced response to antidepressant medication^{2,3} or an increased risk for dementia.⁴ Defined as a reduction of goal-oriented behaviours,⁵ apathy in LLD has been associated with alterations of brain regions involved in executive functions.⁶ However, the functional cerebral underpinnings of apathy in LLD are understudied, applying a unique method on small sample sizes.

Functional magnetic resonance imaging (fMRI) studies of apathy in LLD have been limited to seed-to-whole-brain

analyses derived from 3 regions of interest (ROI), the dorsal anterior cingulate cortex (dACC), the anterior insula and the dorsolateral prefrontal cortex (DLPFC).⁸⁻¹⁰ Apathy has been associated with increased resting-state functional connectivity (rsFC) between the dACC, the anterior insula and orbital cortices, but decreased rsFC with prefrontal lateral regions, as apathy severity increases.⁷ Apathy was also correlated with higher rsFC between the anterior insula and the right DLPFC, mid-cingulate and premotor cortices, and reduced rsFC with the bilateral parietal posterior regions.^{8,9} This hyperconnectivity between the insula and the DLPFC has been associated with treatment nonresponse in individuals with apathy and LLD,⁹ while hypoconnectivity between the

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dACC and DLPFC has been correlated with poorer executive functions¹⁰ and apathy during effortful emotion recognition¹¹ in individuals with LLD. Taken together, these results suggest that apathy in LLD and its traits are underpinned by an altered intrinsic rsFC of the executive network as well as a dysconnectivity of the anterior insula to recruit goal-oriented cognitive and motor processes.^{9,12}

However, these previous studies had 2 main limitations. First, they relied on a few seed regions without investigating the integrity of the cerebral networks they belong to; namely, the default mode, the cingulo-opercular, the somatomotor and the frontoparietal networks.¹³ Dysfunctions of these networks at rest have been implied in the pathophysiology of apathy across neurodegenerative disorders¹⁴ and depression.¹⁵ Yet, choosing few seed regions prevents us from drawing reliable results on the network function contrary to intranetwork rsFC analyses.^{16,17} Second, the aforementioned studies used the Apathy Evaluation Scale¹⁸ (AES) to classify patients with apathy, and this scale has a specificity of only 50%.¹⁹ Moreover, classifying apathy reduced apathy sample sizes to a maximum of 20 per group in these studies by not considering the continuous nature of apathy. Modern assessments like the apathy diagnostic criteria²⁰ (ADC) and the Apathy Motivation Index²¹ (AMI) add a social apathy dimension to the behavioural, cognitive and emotional dimensions of the AES. While the ADC enables a clinician-rated categorization of patients via a diagnostic definition of apathy, the AMI provides a continuous evaluation of apathy, rated by the patient, which has been validated in depression.²¹

In this study, we aimed to identify the subnetworks associated with apathy in LLD in the core resting-state networks (RSN) putatively underlying goal-oriented behaviours. To overcome the limitations from preceding studies, we recruited patients with LLD and assessed apathy using the 3 complementary evaluations to produce generalizable results across apathy measures. Given the lack of data on the neural bases of apathy in LLD, we adopted a cortical ROI-to-ROI functional connectivity analysis to investigate the integrity of the RSN connectivity using a valid brain network parcellation¹³ derived from the multimodal atlas of the Human Connectome Project.²² Our analysis rested upon network-based statistics (NBS), a popular approach to identify subnetworks defined in terms of connected graph components, which offers greater statistical power than traditional correction methods such as false discovery rate correction.²³ However, the original method detects components for edges associated with statistical effects above a predefined threshold set subjectively.²³ In this study, we used a validated method, the threshold-free network-based statistics (TFNBS), which combines NBS with the threshold-free cluster enhancement algorithm.²⁴ The TFNBS method detects components via an adaptive threshold that controls for topological dependency in the data while maintaining sensitivity to strong localized effects.

Our primary aim was to identify the fMRI intranetwork rsFC associated with 3 validated measures of apathy in patients with LLD. We conducted separate analyses for the subnetworks associated with each apathy measure and reported the regions that were common to all 3 measures. Indeed,

there exists no consensual definition of apathy because of theoretical divergences on the nature of this disorder^{18,25} and debated evidence on the validity of the apathy subdomains between the scales.²⁶ Furthermore, each apathy measure has distinct psychometric properties and its own measurement error. The AES is a well-known scale, validated in depression,¹⁸ which conceptualizes apathy as a subjective reduction of motivation and is designed to measure cognitive, behavioural and emotional components of apathy. The AMI measures behavioural activation, which relates to self-initiated and goal-oriented behaviours and emotional sensitivity, and social motivation, which captures engagement in social interactions. Finally, the ADC relies on 3 components of apathy (cognitive, behavioural, and emotional and social) to classify individuals according to the number of components impaired, with a clinical account on the functional impairment induced. Despite the variability between these measures, it has been argued that apathy instruments measure similar core components.²⁶ Hence, we decided to use these 3 tools to measure both common and specific components of apathy. We hypothesized that using 3 apathy measurements would reduce the overall bias due to the measurement error of each individual instrument. Overall, ROI-to-ROI connectivity commonality across the 3 apathy measurements should provide consistent evidence of the cerebral basis of the cognitive, behavioural, social and emotional components of apathy that cause functional impairment. Specifically, we anticipated a decrease in rsFC within the default mode and cingulo-opercular networks, and an increase in rsFC within the frontoparietal network, corresponding to the severity of apathy. Our secondary objectives included testing for inter-network rsFC in the prefrontal brain regions described in a current model of apathy as impaired goal-oriented behaviour¹⁴ and identifying intranetwork rsFC differences between individuals with LLD and healthy controls.

Methods

Participants

We recruited patients with LLD and healthy controls from the French old-age psychiatry centres of Rennes and Tours between October 2019 and April 2022. Inclusion and exclusion were assessed during a psychiatric interview by a trained old-age psychiatrist. Inclusion criteria for the LLD group were age older than 60 years with a major depressive episode assessed using DSM-5 criteria for major depressive disorder²⁷ and the Mini International Neuropsychiatric Interview²⁸ (MINI). Exclusion criteria were any major neurocognitive disorder as per DSM-5 criteria and Mattis Dementia Rating Scale (DRS) score below 125;²⁹ cerebral diseases (e.g., stroke, Parkinson disease, multiple sclerosis); inflammatory or mechanical disease that might alter motor activity (e.g., severe arthritis or spondylitis); severe sarcopenia, defined as a walk test result of less than 1 m/s on the 10 m walk test; extrapyramidal symptoms assessed using the Unified Parkinson's Disease III;³⁰ antipsychotic prescription; high suicidality, defined as a Clinical Global Impression Suicide Scale

score greater than 4; legal protection, deprived of liberty; and MRI contraindication (e.g., pacemaker or metal implants). Healthy controls and patients with LLD were matched for age and education level, as both are confounding factors of apathy. All participants provided written informed consent, and the study was approved by the relevant institutional review board (ID-RCB 2018-AO2643-52, NCT03807167).

Procedure

At inclusion, participants with LLD received a psychiatric evaluation. After inclusion, each participant underwent a neuropsychological assessment as well as a structural and resting-state fMRI scan within the same week.

Clinical assessment

During the psychiatric interview, apathy was assessed using the ADC, the clinician-rated version of the AES and the AMI (Appendix 1, available at www.jpn.ca/lookup/doi/10.1503/jpn.230008/tab-related-content). Depression severity was evaluated with the Montgomery-Åsberg Depression Scale³¹ (MADRS).

To determine their cognitive profile, all participants underwent the same neuropsychological tests administered by trained neuropsychologists. Executive functions were evaluated based on the number of complete categories and preservative errors on the Modified Wisconsin Card Sorting Test³² (MCST) for planning and set-shifting, the Trail Making Test³³ (TMT) A and B-A for speed processing and cognitive flexibility, and the interference score on the Stroop test³⁴ for cognitive control. Language was evaluated based on semantic and phonemic verbal fluency.³⁵

MRI acquisition

All participants underwent MRI on 3T scanners with 64-ch head coils; the same brand and model was used at both sites to reduce between-site variability (Magnetom Siemens Prisma, VE11C, Erlangen, Germany). Whole brain T_1 -weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) images were acquired using the following parameters: repetition time (TR) 1.9 s, echo time (TE) 2.26 ms, inversion time (TI) 900 ms, flip angle 9°, 1-mm isotropic in-plane resolution, field-of-view (FOV) 256 × 256 mm², 176 slabs. During resting-state fMRI scanning, participants were instructed to keep their eyes open, to remain still as much as possible, not to think of anything, and not to fall asleep. Transverse echo-planar imaging (EPI) images with opposite polarities of the phase encoding direction were acquired with the multiband accelerated EPI sequence development release R016a, from the Center for Magnetic Resonance Research with the following parameters: TR 1224 ms, TE 30 ms, flip angle 65°, multiband acceleration factor 3, 2.5-mm² isotropic in-plane resolution, FOV 210 × 210 mm², 54 axial slices with a thickness of 2.5 mm. A total of 288 volumes were collected in 6 minutes, plus 12 seconds for the reversed phase.

Image processing

Preprocessing of anatomic images consisted of skull-stripping using an atlas registration-based method by transforming the structural image of each patient to the atlas image, using the linear and nonlinear block-matching algorithms^{36,37} available in the Anima image processing toolbox (<https://github.com/Inria-Visages/Anima-Public/wiki>).

For the fMRI images, the following preprocessing was performed. The first 4 volumes from each participant were discarded to allow the signal to reach equilibrium and the participants to adapt to the scanning noise. A fieldmap was estimated based on 2 EPI references with opposing phase-encoding directions using TOPUP. The estimated fieldmap was applied to the fMRI images using FUGUE. Head-motion parameters with respect to the median or mean fMRI volume (transformation matrices, and 6 corresponding rotation and translation parameters) were estimated before applying spatiotemporal filtering using MCFLIRT. Blood oxygen level-dependent (BOLD) runs were slice-time corrected using slicetimer. A bandpass filtering was applied to the BOLD signal to filter time series frequencies between 0.01 and 0.1 Hz. The median fMRI volume was coregistered to the participant's structural image using a rigid body transformation model (6 parameters). The structural image was then transformed to the Montreal Neurological Institute (MNI) template using the linear and nonlinear block-matching algorithms.^{36,37} For each participant, 2 image transformations were computed: the transformation from the mean functional volume to the structural volume and the transformation from the individual structural volume to the MNI template. By concatenating the above transformations sequentially, we obtained a direct transformation from each initial functional volume to the MNI space. The inverse of the transformation was applied to the Human Connectome Project (HCP) multimodal parcellation²² to register this atlas in the fMRI native space.

After these steps, nuisance regression was performed with 3 kinds of regressors. Residual motion was removed with the parameters estimated by FSL's MCFLIRT, computed by backward differences (6 regressors). The physiologic noise was reduced using regressors calculated using the CompCor method,³⁸ implemented in Nilearn (<http://nilearn.github.io/>). These 5 regressors correspond to the principal components from noisy regions-of-non-interest, such as white matter, cerebrospinal fluid and non-brain signals. The global signal was included as a regressor by inspection of the connectivity matrix.

Individual structural and functional images were inspected to remove those with significant artifacts or lesions. Participants were excluded if any of the following image quality metrics were above or below the specified threshold. Exclusion criteria were specified as a score greater than 0.025 on the AFNI Quality Index, computed using 3dTqual,³⁹ a signal-to-noise ratio less than 1, and a root-mean-square head motion greater than 2 mm for translations and 1° for rotation, as accepted in elderly populations.^{40,41} With these criteria, 3 patients with LLD were excluded from our analyses: 2 for significant artifacts and 1 for excessive head motion (Appendix 1, Figure S1). Quality metrics for each participant are represented in Appendix 1, Figure S2.

Statistical analysis

Demographic, clinical and psychological data were compared between patients with LLD and apathy and healthy controls based on the ADC using χ^2 tests for qualitative variables as well as independent t tests for normal distribution or the Mann–Whitney U test for non-Gaussian distributions.

Cortical ROIs were selected from the asymmetric HCP atlas,²² originally consisting of 360 ROIs. Following the Cole–Anticevic Brain Network Parcellation,¹³ we investigated the intranetwork connectivity of the default mode (79 nodes), the cingulo-opercular (54 nodes), the somatomotor (38 nodes) and the frontoparietal networks (44 nodes). Following current models of apathy,¹⁴ we defined a subconnectome network of 38 nodes using the same parcellation by selecting the medial regions of all the networks and the orbito-affective network. We hypothesized that limiting the analysis of internetwork connectivity to the relevant ROIs implied in goal-oriented behaviour would enable us to identify the putative stages of the cognitive processes at stake modified with apathy.

The functional connectivity measures between any pair of ROIs were estimated using Pearson correlation. We applied Fisher r -to- z transformation to normalize the coefficients.

To identify the effect of apathy on functional connectivity, we performed TFNBS.^{23,24} This method combines the well-known NBS approach²³ and the threshold-free cluster enhancement algorithm for voxel-wise analysis perfectly adapted for graphs. As in NBS, the algorithm computes the likelihood of each set of connected edges that surpass an initial statistical threshold, also referred to as components of interest (COI). Such likelihood estimation is based on their size (number of connected edges) and how it compares to a null distribution generated by permutations of the original data. However, contrary to NBS, an adaptive threshold was implemented without having to set arbitrary a priori thresholds. The method consists of the 4 following steps (for more details see Baggio and colleagues²⁴): First, the association between the z -scored correlation coefficient of each pair of ROIs and the variable of interest (apathy group, AES score or AMI score) was investigated using 3 distinct linear models, regressing out for age, gender, education and city site. Second, a threshold was applied to the obtained F -statistics matrix at a series of steps h , with a step interval defined as a hundredth of the maximum value of the matrix. Third, at each thresholding step, the value of each matrix suprathreshold element belonging to a connected component was replaced by the component's topological size (number of connections) raised to the power E , multiplied by the component's height raised to the power H . As recommended by Baggio and colleagues,²⁴ the E parameter values were set to 0.75 combined with H parameter values of 3.25. Fourth, the matrices obtained at each step were subsequently summed, giving the final TFNBS score for every network edge. Statistical significance was established through permutation testing over 10000 permutations. At each permutation, group membership or apathy severity score was shuffled across participants, and the above steps were repeated. We obtained family-wise error (FWE)-corrected p values by comparing

each connection's TFNBS score with the null distribution of maximal subconnectome-wise scores at each permutation. As 15 models were performed for apathy (5 networks \times 3 measures of apathy), the α FWE-corrected p value for statistical significance of the network was set at $p = 0.003$.

We present the ROIs belonging to the COI associated with apathy for each apathy measure. We report the marginal mean effect of the ROIs by network and measure as well as the concordant results across the 3 apathy measures. The estimation of the marginal mean effect was performed in 2 steps. First, a linear mixed-effects model was used with the ROI-to-ROI correlation as the response and the interaction between the values of the apathy evaluations and the ROI as fixed effects of interest, adjusted for age, sex and years of education, with the subject as a random intercept. For each ROI, the marginal effect of the apathy measures on correlation was calculated using the `emmeans()` function of the `{emmeans}` package using R Statistical Software version 4.2.1 (R Core Team; 2022). The detailed connectivity matrices for each apathy scale and heterogeneity in ROI-to-ROI identification between the apathy measures are reported in Appendix 1. Results with the MADRS as a covariate are also reported in Appendix 1.

Results

Demographics and clinical measures

Our analyses included 39 patients with LLD and 26 healthy controls from Rennes (26 patients and 13 controls) and Tours (13 patients and 13 controls). Demographic and clinical characteristics of the groups are summarized in Table 1. Twenty-eight of the 39 patients with LLD had a diagnosis of apathy according to the DCA. Patients with and without apathy were similar in terms of age, gender, years of education and executive functions ($p_{\text{uncorrected}} > 0.1$). There were no significant differences between the groups in terms of medication (all $p > 0.1$).

As expected, patients with apathy had more severe depression on the MADRS ($p_{\text{uncorrected}} = 0.03$) than those without apathy. Patients with LLD had similar scores on the DRS as healthy controls ($p_{\text{uncorrected}} > 0.1$). Performance on the cognitive flexibility and verbal fluency tasks were also similar between the groups ($p_{\text{uncorrected}} > 0.1$), but patients with LLD had slower processing speed on the TMT-A ($p_{\text{uncorrected}} = 0.005$) and were more sensitive to interference on the Stroop test ($p_{\text{uncorrected}} = 0.0045$) than healthy controls.

Functional brain components associated with apathy

Default mode network

For DMN intranetwork connectivity, the TFNBS identified 1 component associated with all apathy measures (all $p_{\text{FWE-corrected}} < 0.0001$; Figure 1A and Appendix 1, Table S1). The AES and AMI scores were negatively associated with intranetwork connectivity between the bilateral cingulate pregenual and posterior regions, in the middle and inferior temporal cortices, and in the hippocampal and parahippocampal regions. Apathy was negatively associated with connectivity of pregenual and posterior cingulate regions, and positively

associated with connectivity in temporal regions. The concordant ROIs across the 3 measures of apathy comprised 12 regions belonging to the left presubiculum, the middle temporal lobe, the pregenual anterior cingulate subregion R_p32, the orbital region L_47l, the polar region, the superior lateral prefrontal region, medial prefrontal regions, and middle and posterior cingulate regions (Figure 2).

Frontoparietal network

Within the frontoparietal network, the NBS identified 1 component associated with apathy for each measure of apathy Figure 1B (all $p_{\text{five-corrected}} < 0.0001$, Appendix 1, Table S1). The AMI score was positively associated with intranetwork connectivity between bilateral DLPFC regions and the inferior parietal lobule and precuneus. The AES scores in patients

with apathy were associated with the same regions, but with no global tendency in the direction of the association. The concordant ROIs across the 3 measures of apathy comprised 9 regions belonging to the polar and lateral prefrontal regions, and the superior frontal and inferoparietal cortices (Figure 2).

Cingulo-opercular network

Concerning the cingulo-opercular network, 1 component was associated with AMI ($p_{\text{five-corrected}} < 0.0001$) and AES ($p_{\text{five-corrected}} = 0.003$), but no component was significantly associated with DCA (Figure 1C and Appendix 1, Table S1). Both the AMI and AES were positively associated with intranetwork connectivity between the bilateral dACC, dorsal prefrontal, parietal opercular regions and insula. The concordant ROIs

Table 1: Comparison of demographic and clinical characteristics between patients with LLD with and without apathy, and between patients with LLD and healthy controls

Characteristic	LLD with apathy* n = 28	LLD without apathy* n = 11	Statistic	p value	LLD total n = 39	Control n = 26	Statistic	p value
Age, mean (range), yr	75 (72 to 80)	72 (71 to 78)	$U = 112$	0.19	74 (71 to 80)	75 (72 to 78)	$U = 517$	0.88
Gender, no. M:F	11:17	1:10	$\chi^2 = 2.1$	0.15	12:27	6:20	$\chi^2 = 0.16$	0.69
Education, mean (range), yr	10 (8 to 13)	12 (11 to 15)	$U = 202$	0.13	12 (8 to 15)	11 (9 to 14)	$U = 501$	0.94
Duration of depression, mean (range), yr	23 (8 to 40)	22 (1 to 48)	$t = 0.27$	0.79	23 (1 to 48)	–	–	–
MADRS, mean (range)	27 (25 to 30)	22 (21 to 27)	$U = 85.5$	0.03	25 (21 to 30)	–	–	–
Apathy, mean (range)								
AES	47 (41 to 52)	34 (32 to 39)	$t = -4.8$	< 0.001	42 (32 to 52)	–	–	–
AMI	33 (29 to 36)	20 (18 to 24)	$t = -5.0$	< 0.001	30 (18 to 36)	–	–	–
Psychotropic drugs†, %								
Antidepressant	82	82	$\chi^2 = 0.2$	0.91	82	–	–	–
Mood stabilizer	18	9	$\chi^2 = 0.9$	0.64	15	–	–	–
Benzodiazepine	36	45	$\chi^2 = 0.3$	0.85	38	–	–	–
Antipsychotic	14	0	$\chi^2 = 0.5$	0.46	10	–	–	–
DRS, mean (range)	133 (128 to 137)	136 (132 to 141)	$t = 1.47$	0.18	134 (128 to 141)	–	–	–
TMT-A, mean (range)	51.5 (35.8 to 66.5)	39.0 (35.0 to 51.5)	$U = 119$	0.29	46.0 (35.0 to 66.5)	37.0 (30.0 to 44.0)	$t = 2.4$	0.005
Stroop interference, mean (range)	-73.0 (-91.5 to -51.5)	-73.0 (-106.0 to -60.75)	$U = 103$	0.29	-73.0 (-106.0 to -51.5)	-43.0 (-69.5 to -31.8)	$U = 251$	0.004
Cognitive flexibility, mean (range)								
TMT B-A	72.0 (39.0 to 136.0)	80.0 (69.0 to 100.0)	$t = 0.13$	0.90	79.0 (39.0 to 136.0)	69.0 (41.0 to 103.0)	$t = 1.1$	0.28
MCST perseverative errors	3.0 (2.0 to 6.0)	1.5 (0.3 to 10.0)	$U = 93.5$	0.13	3.0 (0.3 to 10.0)	2.0 (1.0 to 4.0)	$t = 1.5$	0.22
MCST complete categories	6.0 (4.3 to 6.0)	6.0 (4.3 to 6.0)	$U = 127.5$	0.94	6.0 (4.3 to 6.0)	6.0 (5.0 to 6.0)	$U = 398$	0.41
Verbal fluency, mean (range)								
Semantic	22.5 (18.0 to 27.8)	21.0 (14.5 to 24.5)	$U = 193$	0.10	24.0 (14.5 to 27.8)	26.0 (24.3 to 32.0)	$U = 369$	0.12
Phonemic	18.0 (11.5 to 24.0)	21 (14.5 to 24.5)	$U = 164$	0.62	19.0 (11.5 to 24.5)	19.5 (16.3 to 24.0)	$t = -1.2$	0.23

AES = Apathy Evaluation Scale; AMI = Apathy Motivation Index; DRS = Mattis Dementia Rating Scale; F = female; IQR = interquartile range; LLD = late-life depression; M = male; MADRS = Montgomery-Åsberg Depression Scale; MCST = Modified Card Sorting Test; TMT-A = Trail Making test part A; TMT B-A = difference in scores between TMT parts B and A. *Apathy was defined based on the 2018 diagnostic criteria of apathy. †One or more per patient.

across the 2 apathy scales comprised 20 regions belonging to the dACC, midcingulate and posterior cingulate regions; the premotor, frontal opercular and dorsal prefrontal regions; the middle and posterior insula; the parietal opercular regions; and the supramarginal gyrus (Figure 2).

Somatomotor network

After correction of the p value, we did not find significant components associated with AES, AMI or apathy.

Goal-oriented behaviour

Considering brain regions associated with the goal-oriented behaviour model, 1 component was associated with apathy for AES and AMI (all $p_{\text{fwe-corrected}} < 0.003$) measures, but no component was significantly associated with DCA (Figure 1D and Appendix 1, Table S1). The AES was negatively associated with connectivity in the bilateral pregenual and dACC regions, while the AMI was more heterogeneously associated with connectivity across the same regions. The concordant ROIs across

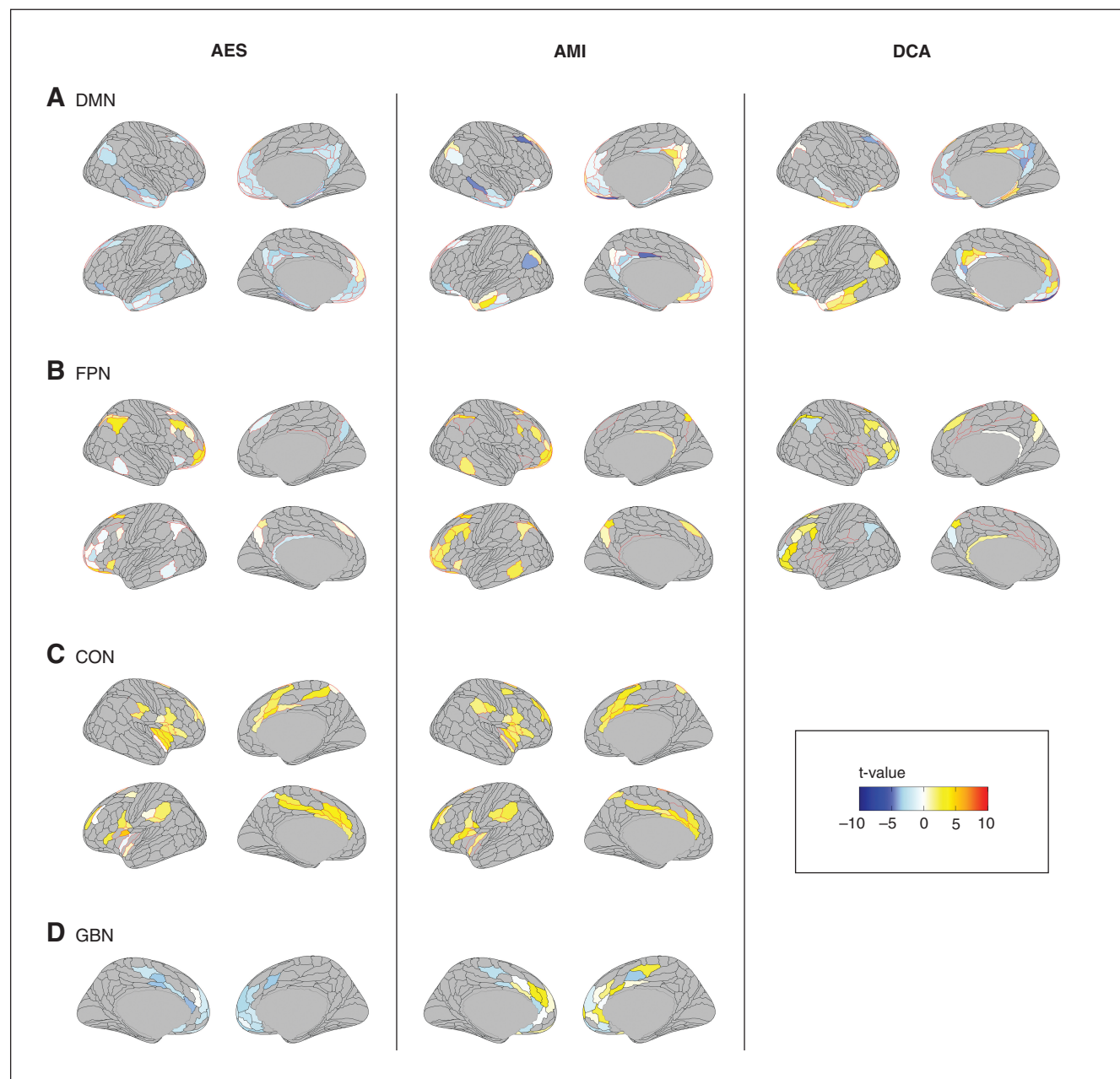


Figure 1: Brain components associated with apathy in late-life depression. Associations between the brain regions whose connectivity was significantly modified for each apathy measure for each resting-state network are represented in colour. AES = Apathy Evaluation Scale; AMI = Apathy Motivation Index; CON = cingulo-opercular network; DCA = diagnostic criteria for apathy; DMN = default mode network; FPN = frontoparietal network; GBN = regions associated with goal-directed behaviours.

the 2 measures of apathy comprised 11 regions belonging to the medial orbital regions; the subgenual, pregenual and dorsal anterior cingulate regions (L_p24, L_a24pr and L_p24pr); and the mid-cingulate and dorsomedial regions (Figure 2).

Discussion

In the present study, we investigated the functional resting-state networks robustly associated with apathy in patients with LLD by combining the concordant results of 3 valid and complementary assessments of apathy. Our main finding was that apathy in patients with LLD was associated with modified rsFC in the networks that support goal-oriented behaviour (DMN, cingulo-opercular, frontoparietal and goal-oriented behaviour networks), but not in the somatomotor network, across apathy scales. However, there were substantial differences in ROI selection and in the direction of the association between rsFC and apathy across the measures. The AES and AMI scores were found to be associated with the 5 networks, while the DCA was associated only with the DMN and the FPN. The AES scores were preferentially associated with reduced intranetwork connectivity of the DMN and the GBN. The AMI scores were mostly associated with increased intranetwork connectivity in the FPN. The DCA was associated with connectivity in the DMN and FPN without a distinct tendency of the association. These discrepancies emphasize the importance of using multiple assessment tools to comprehensively capture the multifaceted nature of apathy in patients with LLD.

In the DMN, apathy was associated with modified rsFC in the ventromedial and temporal regions. The AES had a constant negative association with connectivity between these regions, while the AMI and DCA were associated with a more heterogeneous direction of the association, the decreased connectivity being found only in the pregenual ACC, cuneus and hippocampal regions. The DMN has been robustly associated with pathogenesis of depression.^{42,43} The

temporal regions we identified belong to the medial temporal lobe subsystem of the DMN, which is believed to support spontaneous thought and expectation about the future.⁴⁴ Our results confirm those of previous studies in depression that found that apathy was associated with rsFC in the pregenual anterior cingulate regions and ventromedial prefrontal cortex,⁴⁵ suggesting impaired emotion regulation in individuals with apathy and depression.⁴⁶ While we identified very similar ROIs associated with apathy to previous results on the topic, the directions of the associations we observed were different from those reported in the studies using seed-based approaches.^{9,47,48} These differences might be related to the use of few seeds in previous studies omitting the variability between ROI connectivity within a same RSN. Our findings suggest that the AES might provide a more consistent measure of modified intranetwork connectivity in the DMN in individuals with apathy.

Participants with apathy had modified rsFC within the frontoparietal network, also referred to as the executive control network. The AMI was consistently associated with an increased rsFC in the middle frontal gyrus regions, frontopolar cortex, temporal cortex and anterior angular gyrus. Conversely, the AES was associated with reduced connectivity in the DLPFC, while the DCA was associated with a reduced connectivity in the angular gyrus. Anomalous rsFC between the middle frontal gyrus and parietal cortex has been consistently reported in individuals with symptoms of social anxiety,⁴⁹ with an increased activity of these regions in those with pathological anxiety across disorders. These regions have been implicated in anxiety regulation,⁵⁰ notably in the context of social anxiety.^{51,52} Moreover, the association between the DCA and parietal cortex activity suggests that FPN connectivity may be linked to functional impairment in individuals with apathy. The frontal and parietal regions implicated in these 3 apathy measures are known to be involved in executive functions such as decision making, conflict resolution and language recognition.^{51–55} Executive dysfunctions are

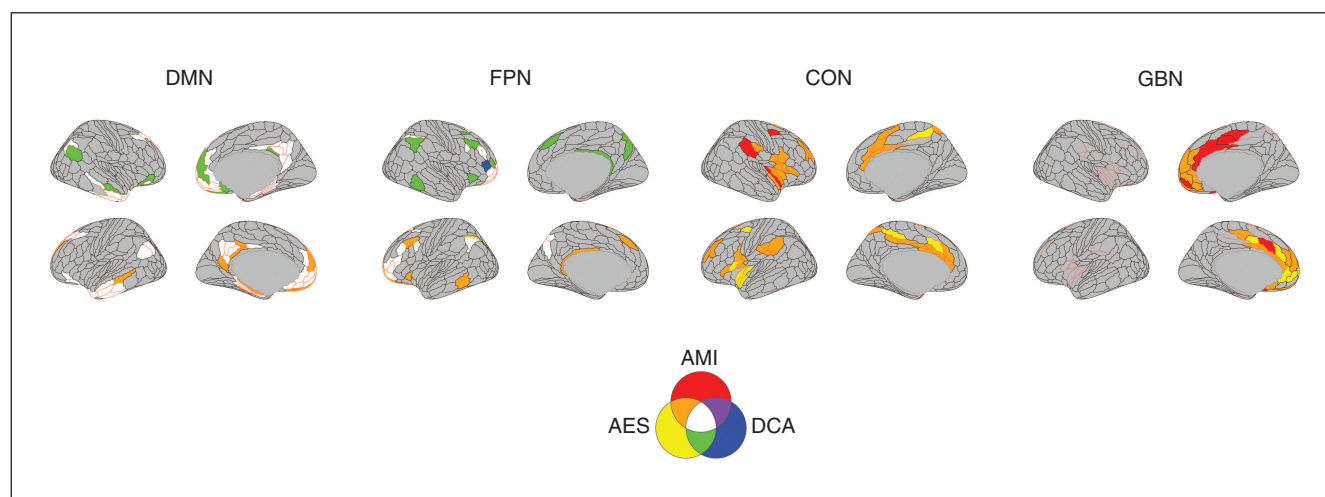


Figure 2: Brain regions common to the different apathy measures. The brain regions identified as being associated with apathy across the measures are represented in colour. AES = Apathy Evaluation Scale; AMI = Apathy Motivation Index; CON = cingulo-opercular network; DCA = diagnostic criteria for apathy; DMN = default mode network; FPN = frontoparietal network; GBN = regions associated with goal-directed behaviours.

core cognitive impairments in individuals with LLD^{6,56–58} and have been robustly associated with apathy.^{59,60} Therefore, the expected association between apathy and frontoparietal network connectivity aligns with previous research. Increased rsFC of the executive control network was found to be correlated with greater depression severity, greater anhedonia, poorer performance on tests of executive function and working memory in LLD¹⁰ and with apathy in women with LLD.¹¹ On the other hand, some studies reported an association between lower rsFC within the executive control network and severity of apathy in LLD.^{9,47} These discrepancies may stem from variations in the seed regions used to define the executive control network, ranging from the DLPFC to the dACC.

We observed that severity of apathy, as measured using the AES and AMI, was linked to increased rsFC within the cingulo-opercular network. Specifically, the dACC (a24pr) and inferior parietal cortices emerged as central hubs within the cingulo-opercular network component, consistent with previous findings.⁸ Additionally, we found enhanced connectivity between the right insula and the DLPFC, which aligns with previous reports.^{8,9} The insula is known to play a crucial role in salience detection, task switching and behaviour adaptation through recruitment of the cognitive control network.^{61,62} Given that the insula and dACC are involved in emotional reactivity, particularly in fear conditioning,⁵⁰ the identified subnetwork may indicate impaired processing of emotional salience in apathy associated with LLD. However, we identified no connectivity pattern associated with the DCA, which could be attributed to either a lack of involvement of the cingulo-opercular network in functional impairment associated with apathy or to limited statistical power to detect such an association.

We found modified rsFC in the regions associated with goal-oriented behaviour in patients with LLD and apathy. The AES was negatively associated with connectivity in the bilateral pregenual and dACC regions, while the AMI was more heterogeneously associated with connectivity across the same regions. These findings align with a model of apathy supporting dysfunctional interactions among the brain regions underlying motivated behaviour, derived from observations in neurodegenerative and vascular disorders.^{5,14} This model reports constant alterations of the prefrontal medial regions underpinning stimuli valuation in ventral areas, behaviour adaptation in cingulate regions and motor execution in dorsal regions^{63,64} in individuals with apathy. Specifically, we observed modified rsFC in pregenual cingulate regions, which have been proposed as a potential substrate for treatment-resistant depression;⁶⁵ ventromedial regions implicated in stimuli valuation; and dACC and frontopolar regions, which have been implicated in behaviour adaptation. These results suggest disruptions in the valuation and adaptive systems in patients with LLD and apathy, with variations depending on the inclusion or exclusion of a social dimension. Interestingly, the consistent negative association between the AES, goal-oriented behaviour network and the DMN suggests that this scale might measure with more sensitivity the deficit in goal-oriented behaviour associated with emotion regulation and context valuation. However, we did not find a significant component associated with the diagnosis of apathy,

indicating that the DMN may not be directly implicated in the functional impairment caused by apathy.

We did not find any significant component within the somatomotor cortex associated with apathy after *p* value correction. To our knowledge, no study had previously explored the intranetwork rsFC of the somatomotor network in patients with LLD. However, reduced connectivity between the dACC and regions of this network have been reported in patients with LLD and apathy,⁹ implicating the premotor cortex and paracentral lobule. Taken together, apathy in LLD seems not to be associated with modified intranetwork rsFC of the somatomotor cortex.

Compared with healthy controls, patients with LLD had altered intranetwork rsFC in the DMN, the cingulo-opercular network and the frontoparietal network. Within the DMN, our exploratory results suggest that LLD was associated with lower overall rsFC, as previously reported.¹⁰ The parahippocampal cortex and the hippocampal formation had greater connectivity with frontopolar and dorsolateral regions of the DMN in patients with LLD, suggesting hyperactivity of the limbic system also previously reported.^{15,66} Within the cingulo-opercular network, depression was associated with reduced intranetwork rsFC. Two hubs stood out in the component, the insula and the mid-DLPFC, as reported previously.⁸ The alterations of the FPN component in patients with LLD is consistent with the literature,^{47,48} with dysconnectivity of the DLPFC and of lateral parietal regions.

Limitations

This study has several limitations. First, our analysis focused solely on cortical intranetwork connectivity, which may explain the divergent findings compared with previous studies that involved seed-to-whole-brain analyses including subcortical regions. Additionally, the use of global signal regression, unlike in prior studies, could account for some of the differences observed in the direction of functional connectivity changes.

Second, our study design did not achieve a balanced recruitment of patients with and without apathy according to the ADC. Consequently, our sample consisted of a larger proportion of participants with apathy, which might have diminished the likelihood of detecting rsFC components specifically associated with the diagnosis of apathy. Therefore, the small effect sizes observed in the brain components linked to apathy diagnosis, as well as the absence of components found in the cingulo-opercular network and the regions associated with goal-oriented behaviour, could be primarily attributed to a lack of statistical power rather than underlying pathophysiological mechanisms. Despite the observed gender imbalance within the apathy and LLD groups, we included sex as a covariate in all statistical analyses. It is important to note that, compared with those for depression, the clinical criteria for apathy are relatively recent and still in the process of validation.

We aimed to partially address the limitations of using the DCA by reporting the shared ROIs associated with the 3 apathy measures. This allowed us to reduce classification bias associated with DCA and identify brain areas associated with the

well-established scales of apathy (AES and AMI) as well as those associated with apathy-related functional impairment. However, caution should be exercised when interpreting the overlap between brain regions, as it is specific to the apathy measures used and may not be extrapolated to other apathy scales. Furthermore, although all apathy measures aim to evaluate a common construct, each evaluation differs in terms of purpose, theoretical framework and psychometric properties,²⁶ which may have contributed to the difference between the networks associated with each apathy measure. The inclusion of recordings of daily activity, such as data from accelerometers, could offer a more objective characterization of apathy than clinical ratings. As a future direction, we plan to replicate this study using accelerometer data to further enhance the understanding of apathy.

Conclusion

Our study suggests that disturbances in functional connectivity among the core set of brain networks that support motivated behaviour are consistently associated with apathy, regardless of the clinical evaluation chosen. These results confirm those of previous studies while underscoring the necessity of using multiple assessment tools to capture the multifaceted nature of apathy in patients with LLD. Future studies combining multimodal neuroimaging data and behavioural recordings could improve the understanding of apathy in patients with LLD.

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Chapter 9

Study 2

OVERVIEW

This study addresses the following question: what are the relationships between motor activity, apathy and the underlying brain connectivity in LLD? We found that two principal components of motor activity were significantly associated with apathy. The first principal component (PCA1), corresponding to overall diurnal motor activity, was negatively associated with AES scores while the second principal component (PCA2), corresponding to early chronotype, was negatively associated with AMI scores. Regarding intra-network resting-state functional connectivity, PCA1 was associated with increased connectivity within the default-mode, the cingulo-opercular and the frontoparietal network, while PCA2 was associated with more heterogenous connectivity between both hemispheres of the same regions. However, we did not find significant associations between microstructural metrics of white matter and patterns of motor activity. Taken together, these innovative results suggest that motor activity patterns and their associated functional neural connectivity play a pivotal role in understanding the complex interplay between apathy and LLD. The manuscript has been submitted in Biological Psychiatry Cognitive Neuroscience and NeuroImaging.

Quantifying Apathy in Late-Life Depression: Unraveling Neurobehavioral Links through Daily Activity Patterns and Brain Connectivity Analysis

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ABSTRACT

Background. Better understanding apathy in late-life depression (LLD) would help predicting pejorative course of the disease such as dementia. Actimetry provides an objective and ecological measure of apathy from patients' daily motor activity. We aimed to determine if patterns of motor activity were associated with apathy and brain connectivity in networks underlying goal-directed behaviors.

Methods. Resting-state functional MRI and diffusion MRI were collected from 38 non-demented LLD subjects. Apathy was evaluated using the diagnostic criteria for apathy, the apathy evaluation scale (AES) and the apathy motivation index (AMI). Functional principal components (fPC) of motor activity were derived from actimetry recordings of 72 hours. Associations between fPC and apathy were estimated by linear regression. Subnetworks whose connectivity was significantly associated with fPC were identified via the threshold-free network-based statistics. The relationship between apathy and microstructure metrics was estimated along fibers by diffusion tensor imaging and a multicompartiment model called neurite orientation dispersion and density imaging via tractometry.

Results. We found two fPC associated with apathy: mean diurnal activity, negatively associated with AES, and an early chronotype, negatively associated with AMI. Mean diurnal activity was associated with increased connectivity in the default-mode, the cingulo-opercular and the frontoparietal networks, while chronotype was associated with a more heterogenous connectivity pattern in the same networks. We did not find significant associations between microstructural metrics and fPCs.

Conclusion. Our findings suggest that mean diurnal activity and chronotype are behavioral markers of apathy in LLD, associated with modified functional connectivity of brain networks underlying goal-directed behaviors.

Keywords: Geriatric Psychiatry, Major Depressive Disorder, Apathy, Accelerometry, Resting-State Functional Imaging (rs-fMRI), Diffusion-Weighted Imaging (DWI), Network Analysis

LIST OF ABBREVIATIONS

- 1
2
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4
5 ACC: Anterior cingulate cortex
6
7 AES: Apathy evaluation scale
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9 AMI: Apathy motivation index
10
11 dACC: Dorsal anterior cingulate cortex
12
13 DLPFC: Dorso-lateral prefrontal cortex
14
15 dMRI: Diffusion MRI
16
17 DRS: Mattis dementia rating scale
18
19 DSM-5: Diagnostic and Statistical Manual of Mental Disorders, fifth version
20
21 DTI: Diffusion Tensor Imaging
22
23 FA: Fractional Anisotropy
24
25 fMRI: functional magnetic resonance imaging
26
27 fPC: Functional Principal Component
28
29 fPC1: first principal component of motor activity
30
31 fPC2: second principal component of motor activity
32
33 FWE: Family-wise error
34
35 HC: Healthy control
36
37 LLD: Late-life depression
38
39 MADRS: Montgomery-Asberg depression rating scale
40
41 MCST: Modified card sorting test
42
43 MD: Mean Diffusivity
44
45 MME: Marginal Mean Effects
46
47 NODDI: Neurite orientation dispersion and density imaging
48
49 ODI: Orientation Dispersion Index
50
51 ROI: Region of interest
52
53 RSN: Resting State Network
54
55 rsFC: Resting-state functional connectivity
56
57 TFNBS: Threshold-free network-based statistics
58
59 TMT-A: Trail A of the Trail Making test
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61 TMT B-A: Difference in scores between versions B and A of the Trail
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1. Introduction

Late-life depression (LLD) represents a public health concern given its high prevalence and detrimental impact on the well-being (1,2). Apathy, defined by diminished motivation, reduced interest and lack of engagement in activities (3,4), has been linked to poorer treatment outcomes (5,6) and an elevated risk of dementia in LLD (4,7). A deep understanding of the brain mechanisms underlying apathy in LLD is crucial to better stratify individuals suffering from LLD and prevent the pejorative trajectory associated with apathy. To do so, an accurate measurement of apathy in LLD that goes beyond self-reported and hetero-questionnaires is required. Questionnaires suffer from a lack of accuracy in measuring the goal-directed behaviors related to brain mechanisms, affecting their construct validity, (8,9) and are possibly biased by cognitive impairment and altered self-awareness (10).

Accelerometry, a method for quantifying physical activity using wearable devices, offers an opportunity to objectively assess behavioral engagement in activities in real-world settings. Principal component analysis (PCA) of daily activity is a simple method to estimate patterns of motor activity associated with apathy course in dementia and psychiatric disease. Apathetic patients with Alzheimer's disease exhibited earlier waking and bedtime schedules, as well as a bimodal diurnal activity, compared to non-apathetic patients (11). These motor patterns were also associated with mild-cognitive impairment (12) and predictive of decrease cognition performance in community elderly (13).

Coupling accelerometry measurements with neuroimaging techniques, such as structural and resting-state functional magnetic resonance imaging (rs-fMRI), could provide an objective multidimensional examination of the neural correlates of apathy. Apathy has been associated with increased resting-state functional connectivity (rsFC) between the anterior cingulate cortex (ACC), the anterior insula and orbital cortices but decreased rsFC with prefrontal lateral regions (14–16). Higher rsFC between the anterior insula and the right dorsolateral prefrontal (DLPFC) and premotor regions but reduced rsFC with the bilateral parietal posterior regions was also correlated with apathy (17,18). In LLD, this hyperconnectivity between the insula and the DLPFC is associated with treatment non-response in apathy (15), while hypoconnectivity between the dorsal ACC (dACC) and DLPFC is correlated with poorer executive functions (19) and apathy during effortful emotion recognition (20). Diffusion MRI (dMRI) studies could also help to better detect white-matter microstructure modifications specifically associated with depression dimensions (21), such as apathy. In LLD, reduced anisotropy of the splenium of the corpus callosum, cingulum, and fronto-occipital fasciculus have been associated with apathy (15). These results suggest that apathy in LLD is underpinned by modifications in functional and structural connectivity of goal-oriented networks. However, it remains unclear if objective patterns of motor activity in LLD could capture impaired connectivity in these networks.

We propose to integrate brain connectivity and accelerometry to unravel the neural mechanisms underlying apathy in LLD. To this end, we recorded the motor activity of LLD participants during three complete days. We estimated the association between accelerometry principal component scores of

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motor activity and apathy clinical scores. Then, we aimed to identify the rsFC subnetworks and structural white-matter lesions associated with the apathy-related motor components. We hypothesized that comparable patterns of physical activity, akin to those outlined in apathy in dementia, were correlated with the functional and structural networks underlying goal-oriented behaviors. This study is a continuation of a previous study investigating association between apathy and rsFC in LLD (16).

2. Materials and methods

2.1 Participants

Thirty-nine LLD patients were recruited from the French old-age psychiatry centers of Rennes (26 subjects) and Tours (13 subjects) between October 2019 and April 2022. Inclusion and exclusion criteria were assessed during a psychiatric interview by a trained old-age psychiatrist. Inclusion criteria were: age > 60 years old with DSM-5 and Mini International Neuropsychiatric Interview criteria of major depressive disorder. Non-inclusion criteria comprised: DSM-5 criteria for major cognitive disorder and Mattis Dementia Rating Scale (MDRS) < 125; neurological diseases; inflammatory or mechanical disease impeding motor activity; severe sarcopenia defined as a walk test < 1m/second; extrapyramidal symptoms assessed at the Unified Parkinson's Disease III; anti-psychotic prescription; high suicidality defined as a Clinical Global Impression Suicide Scale > 4; legal protection, deprived of liberty; and MRI contraindication. Written informed consents were collected. The study was approved by the relevant institutional review board (ID-RCB 2018-AO2643-52, [NCT03807167](#)).

2.2 Procedure

After inclusion, each participant underwent a neuropsychological assessment, and their motor activity recorded during 72 hours using an accelerometer (wGT3X-BT, ActiGraph®) worn at the non-dominant wrist. The last day of recording, patients underwent a structural and rs-fMRI scan.

2.2.1 Clinical assessment

During the psychiatric interview, apathy was assessed by the diagnostic criteria for apathy (DCA) of the 2018 international consensus group (9) the clinician-rated version of the apathy evaluation scale (AES) (22) and the apathy motivation index (AMI) (23). These measures provide complementary evaluation of apathy, the AES evaluating the cognitive, behavior and emotional dimensions of apathy, the AMI exploring the social dimension of apathy, and the DCA considering the functional impairment caused by apathy. Depression severity was measured via the Montgomery-Åsberg Depression Scale (24) (MADRS).

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Participants' cognitive profile was established by trained neuropsychologists. Executive functions were evaluated by the Modified Wisconsin Card Sorting Test ((25)) for planning and set-shifting, the Trail Making Test ((26)) A and B for speed processing and cognitive flexibility, and the Stroop test for cognitive control ((27)). Language was evaluated via semantic and phonemic verbal fluencies ((28)).

2.2.2 MRI acquisition

All participants underwent MRI on 3 Tesla scanners of the same brand and model at both sites to reduce between-site variability. Whole brain T1-weighted was acquired by magnetization prepared rapid gradient echo with repetition time (TR) = 1.9 sec, echo time (TE) = 2.26 msec, inversion time (TI) = 900 msec, flip angle = 9°, 1 mm isotropic, field-of-view (FOV) = 256·256 mm², 176 slabs. Transverse rs-fMRI echo-planar images aligned with the anterior and posterior commissures, were acquired with the following parameters: TR = 1224 msec, TE = 30 msec, flip angle = 65°, multiband acceleration factor 3, in-plane resolution = 2.5x2.5 mm² isotropic, FOV = 210 · 210 mm², 54 axial slices with a thickness of 2.5 mm and an anterior-posterior phase encoding direction. A total of 288 volumes were collected as well as a few reversed phase encoding volumes for distortion correction. Diffusion weighted MRI were acquired by a 60-gradient multishell Cube and Sphere sequence (29) with 2 mm isotropic resolution, TR = 5216 msec, TE = 54.4 msec, multiband acceleration factor 2, parallel imaging with GRAPPA 2, FOV = 220 · 220 mm², 72 axial slices and an acquisition matrix size of 110·110, 6/8 partial Fourier, 60 gradient orientations with b values ranging from 0 to 3000s/mm² and 7 b₀ with an anterior-posterior phase encoding direction and an additional b₀ with reversed (P>A) phase encoding.

2.3 Image processing

2.3.1 Preprocessing of accelerometry data

Preprocessing of accelerometry is detailed in **Supplementary Methods**. To summarize, accelerometer data was measured every 30-second interval between 5 a.m and midnight during 72 hours. One subject was excluded due to insufficient recording. Daytime motor activity was smoothed from a selected model, to account for the short recording period. Functional principal components (fPC) of activity were calculated from the predictions of the selected model using singular value decomposition. The fPC eigenfunctions provided a qualitative representation of interindividual variations in activity patterns while eigenvalues summarized quantitatively these variations (30) . The top four fPC were selected (30). Individual scores for each component were calculated, summarizing the subject's mean variation at each fPC.

2.3.2 Preprocessing of MRI data

Details of the preprocessing of T1-weighted images, fMRI and diffusion data are reported in **Supplementary Methods**.

2.3.3 Brain regions of interest

For fMRI data, cortical regions of interest (ROIs) were selected from the asymmetric human connectome project (HCP) atlas (30) consisting of 360 ROIs. Following the Cole-Anticevic brain-network parcellation (29), we investigated the intra-network connectivity of the default mode, cingulo-opercular and fronto-parietal networks.

For dMRI data, white-matter segmentation was performed based on a convolutional neural network that segments tracts in fields of fiber orientation distribution function peaks, pretrained on high-quality diffusion images acquired for the HCP, implemented in TractSeg (33). This algorithm was applied on preprocessed diffusion data after a rigid alignment on the MNI template. Based on previous studies on LLD or apathy (34–36), we selected a priori 22 bundles of interest: 7 parts from the corpus callosum comprising the rostrum (CC_1), genu (CC_2), posterior midbody (CC_3), isthmus (CC_4), and splenium (CC_5), the anterior commissure (AC), bilateral cingulum (CG), bilateral superior longitudinal fascicles (divided in 3 parts: SLF_I, SLF_II, SLF_III), bilateral inferior longitudinal fascicles (ILF), bilateral corticospinal tracts (CST), and bilateral uncinate fascicles (UF).

2.3.4 Diffusion Model

Two water diffusion models were estimated: diffusion tensor imaging (DTI) and neurite orientation dispersion and density imaging (NODDI). The classical DTI model is calculated on the 30 diffusion-encoding gradients on a shell at $b = 1000$. Fractional anisotropy (FA) and mean diffusivity (MD) scalar maps were derived from DTI (37). In NODDI, the diffusion signal is decomposed into two compartments: an anisotropic compartment corresponding to the intra-neurite space and an anisotropic Gaussian space related to extra-neurite compartment including cell bodies (38). The NODDI-derived metrics are intracellular volume fraction corresponding to neurite density and the orientation dispersion index (ODI) representing angular variation of neurites.

2.4 Statistical analyses

2.4.1 Participants characteristics

Demographic, clinical and psychological data were compared between apathetic and non-apathetic LLD using chi-2 tests for qualitative variables and independent t-tests otherwise (or Mann-Whitney test if distributions were non-gaussian).

2.4.2 Association between daily activity and apathy scores

Three multiple linear regression models were performed with the apathy score as the dependent variable (AES, DCA or AMI), and the fPC scores of accelerometry as independent variables (four components)

1 with age, sex and years of education as covariates. The p-value was set as 0.05/3 (number of networks
2 tested).

3 4 5 **2.4.3 Association between daily activity and resting-state network functional connectivity**

6 Functional connectivity between ROIs was assessed using Pearson's correlation, normalized through r-
7 to-z transformation. The association between fPC of motor activity and rsFC was estimated via
8 threshold-free network-based statistics (TFNBS) (39,40, detailed in **Supplementary Methods**). This
9 method combines the network-based statistics approach (40) and the threshold-free cluster enhancement
10 algorithm. It computes the likelihood that a set of connected edges associated with a variable surpasses
11 a range of statistical thresholds, without having to choose an arbitrary threshold. The association
12 between connectivity and fPC scores was corrected for age, gender and education by linear regression.
13 Statistical significance was established through permutation testing over 10000 permutations. FWE-
14 corrected p-values were obtained by comparing each connection's TFNBS score with the null
15 distribution of maximal sub-connectome- wise scores at each permutation. P-value for statistics
16 significance of the network was set as 0.05/3.

17 While TFNBS provides a score to identify the significant subnetwork associated with a variable, it does
18 not give the direction of the association. For interpretation, we reported the marginal mean effect (MME)
19 at each ROI level. MME are conditional averages, corresponding to the expected change in correlation
20 for a ROI with all others ROIs for an increase of fPC scores, holding other predictor variables constant
21 (41). To do so, a linear mixed model effect was applied on the subnetwork detected by TFNBS with the
22 ROI-to-ROI correlation as the response, the interaction between the values of the apathy evaluations
23 and the ROI as fixed effects of interests, adjusted on age, sex, years of education, and with the subject
24 as a random intercept.

25 26 27 28 29 30 31 32 33 **2.4.5 Association between daily activity and diffusion MRI**

34 For each bundle, the center line of the tract was computed using the minimum-distance-flipped metric
35 (42) and resampled to 100 equidistant segments. Microstructure metrics were projected on the center
36 line via a cKDTtree algorithm (42). The association between the fPC scores of motor activity and
37 diffusion metrics along the bundle was evaluated using a linear model with age, sex and center as
38 covariates. At each tract point, we used a nonparametric permutation-based statistical comparison with
39 5000 iterations to account for multiple comparisons given the correlative structure between adjacent
40 points and the number of tracts tested (43). We report the number of clusters whose size exceeds the
41 specified threshold with adjustment for the number of tracts and points.

	LLD Apathetic (n = 27)	LLD Non-apathetic (n = 11)	Statistics	p-value	LLD Total (n = 38)
Age (years)	75 72 – 81	72 71 – 78	t = 1.22	p = 0.23	74 72 – 80.75
Gender (M:F)	11:16	1:10	$\chi^2 = 2.31$	p = 0.13	12:26
Education (years)	10 8 – 12.5	12 11 - 15	t = -1.61	p = 0.13	12 8 – 13.75
Medical comorbidities					
Cardiovascular	11%	18%	$\chi^2 = 0.26$	p = 0.61	13%
Neurological	0%	0%			0%
Pneumological	4%	10%	$\chi^2 = 0.40$	p = 0.52	16%
Rhumatological	11%	27.3%	$\chi^2 = 1.06$	p = 0.30	5%
Depression characteristics					
Type of depression (MDD : Bipolar disorder)	21:6	10:1	$\chi^2 = 0.01$	p = 0.92	31:7
Duration of depression (years)	25 7 - 40	22 1 - 48	U = 119	p = 0.85	24 4 – 40
MADRS	27 25 - 30	22 21 - 27	t = 1.94	p = 0.06	25 22 – 30
Apathy					

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AEES	48 40 – 52	34 32 – 39	$t = 3.72$	$p < 0.001$	42 37 – 50
AMI	33 29 – 36	20 18 – 24	$t = 4.82$	$p < 0.001$	30 18 – 36
Psychotropic drugs (1 or more per subject)					
Antidepressants	85%	82%	$\chi^2 = 0.25$	$p = 0.88$	84%
Mood Stabilizers	15%	9%	$\chi^2 = 0.47$	$p = 0.79$	13%
Benzodiazepines	37%	45%	$\chi^2 = 0.23$	$p = 0.89$	39%
Antipsychotic	15%	0%	$\chi^2 = 0.58$	$p = 0.44$	11%
Cognitive Evaluation					
DRS	132 128 – 136	136 132 – 141	$t = -1.20$	$p = 0.24$	134 128 – 137
TMT-A	54 36.5 – 67.0	39.0 35.0 – 51.5	$U = 108.5$	$p = 0.20$	47.5 36.0 – 64.8
Stroop interference score	-73.5 -92.3 – -54.0	-73.5 -106.0 – -60.75	$U = 103.5$	$p = 0.36$	-73.5 -97.3 – -54.8
TMT B-A	76.0 48.8 – 139.5	80.0 69.0 – 100.0	$U = 127$	$p = 0.89$	80.0 57.0 – 124.0
MCST perseverative errors	3.5 1.8 – 6.0	1.5 0.3 – 3.0	$U = 79$	$p = 0.12$	3.0 1.0 – 5.8

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MCST Complete categories	6.0 4.0 – 6.0	6.0 4.3 – 6.0	U = 124.5	<i>p</i> = 1	6.0 4.0 – 6.0
Verbal Fluencies					
Semantic	22.0 18.0 – 27.0	26.0 22 – 29.9	<i>t</i> = -2.21	<i>p</i> = 0.03	23.5 18.0 – 28.3
Phonemic	18.0 10.8 – 23.8	21 14.5 – 24.5	<i>t</i> = -0.57	<i>p</i> = 0.58	18.0 13.0 – 24.0

Table 1. Demographic and clinical data in apathetic and non-apathetic LLD groups

The entire LLD group was used for further analyses. Here, we present the apathetic and non-apathetic depression groups, based on the diagnostic criteria of apathy, to describe the participants characteristics with and without significant apathy impacting functioning.

Summary descriptive results: Mean, minimum – maximum. **Acronyms:** AES: Apathy Evaluation Scale; AMI: Apathy Motivation Index; LLD: Late-Life Depression participants; MCST: Modified Card Sorting Test; MDRS: Mattis Dementia Rating Scale; TMT-A: Trail A of the Trail Making test; TMT B-A: difference in scores between versions B and A of the Trail.

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3. Results

3.1 Demographics and clinical measures

Demographic and clinical variables of the LLD group (apathetic and non-apathetic) and HC are reported in Table 1. Twenty-seven LLD participants met the DCA criteria of apathy against eleven non-apathetic LLD. Both groups had a majority of unipolar depression, with similar proportions between the groups and an increased depression severity tendency in the apathetic group ($p_{\text{uncorrected}}=0.06$). Apathetic and non-apathetic groups were similar in terms of age, gender, years of education and executive functions ($p_{\text{uncorrected}}>0.1$) except for phonemic fluencies ($p_{\text{uncorrected}}=0.03$). We did not find significant differences between the groups in terms of medication and medical comorbidities (all $p>0.1$).

3.2 Association between patterns of activity and apathy in LLD

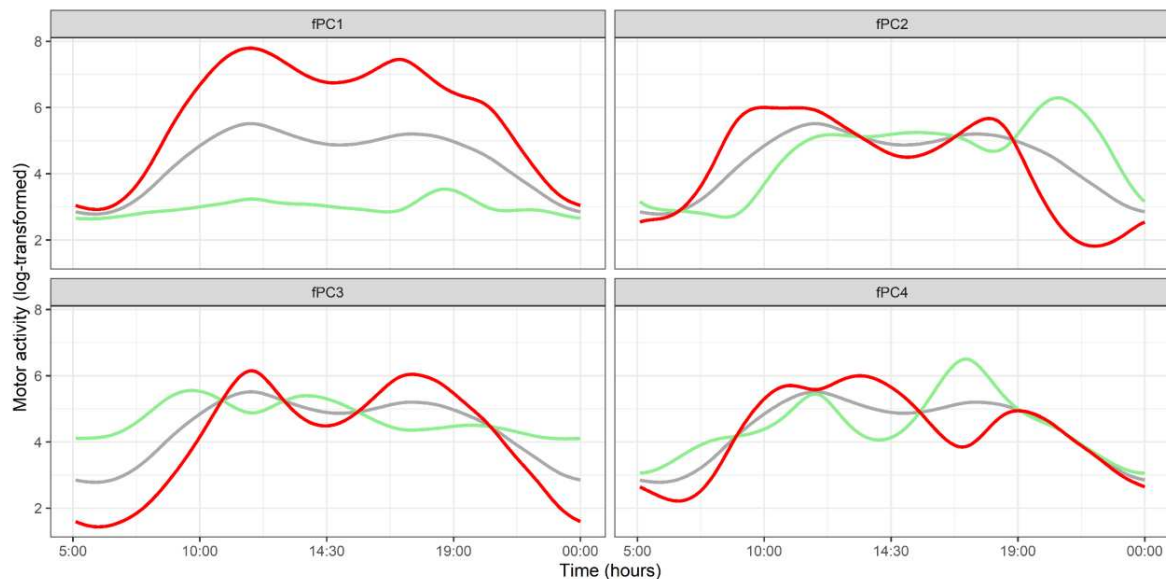


Figure 1. Functional principal components of motor activity in LLD

The first four components of the functional principal component analysis (fPC) of actimetry. The principal component functions are shown as perturbations of the mean activity (grey). The red curve shows what happens when a small amount of a principal component is added to the mean. Similarly, the green curve shows what happens when a small amount of a principal component is subtracted.

The first four components of motor activity, explaining 85% of total variance, are presented **Figure 1**. The first functional principal component (fPC1), accounting for 51% of the variance, identifies participants' mean daily activity. The second functional principal component (fPC2), explaining 16% of the variance, distinguishes participant with high morning activity and reduced evening activity (red curve), from participants with reduced morning activity and high evening activity (green curve). The

third functional principal component (fPC3), explaining 13% of the variance, distinguishes individuals with low activity at waking and before sleeping, associated with a bimodal activity, (red curve) against individuals with higher baseline and constant diurnal activity. The fourth functional principal component (fPC4), capturing 6% of the variance, identifies a pattern with high activity in early-afternoon and low activity in late-afternoon from subjects with low activity in early-afternoon and high activity in late-afternoon.

Regarding the associations with apathy (**Table 2**, significant results $p < 0.017$), we found a significant association between fPC1 and AES (z -value=-3.37, $p=0.002$) and a tendency with DCA (z -value=-2.50, $p=0.018$) suggesting that apathy severity is associated with a reduced mean activity; but not with the AMI ($p=0.07$). The fPC2 scores were negatively associated with the AMI (z -value=-2.78, $p=0.016$) but not with the other measures (all $p > 0.05$), suggesting that apathetic individuals exhibit decreased motor activity during the morning and higher activity in the evening. We found no significant association between apathy and fPC3 nor fPC4.

Apathy Measures	fPC1		fPC2		fPC3		fPC4	
	t-value	p-value	t-value	p-value	t-value	p-value	t-value	p-value
AES	-3.37	0.002	-1	0.3	1	0.3	0.2	0.2
AMI	-1.89	0.07	-2.53	0.016	0.78	0.4	-2.1	0.04
DCA	-2.5	0.018	-1.9	0.07	-0.7	0.48	-2.1	0.04

Table 2. Associations between principal components scores and apathy

Statistically significant associations between functional principal components (fPC) and apathy measures are reported in bold. Significant p -value had to be less than 0.017 (0.05/3) to correct for the number of apathy variables tested. **Acronyms:** AES: Apathy Evaluation Scale; AMI: Apathy Motivation Index; DCA: Diagnostic Criteria for apathy, fPC#, functional principal component number #.

3.3 Association between motor activity and resting-state fMRI intranetwork connectivity in LLD

Association between the first principal component of activity and brain intranetwork functional connectivity

The statistically significant results are reported in **Figure 1A** and **Supplementary Table S2**.

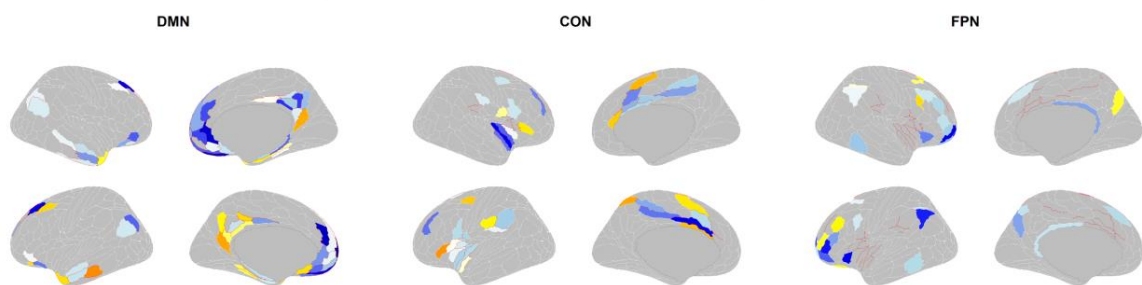
For the DMN, we identified with TFNBS one subnetwork associated with fPC1 scores (all $p_{\text{fwe-corrected}} < 0.0001$). Connectivity between regions of this subnetwork containing medial, latero-inferior and superior prefrontal regions, inferior temporal regions, posterior cingulate and cuneus, as well as infero-

parietal cortices was negatively associated with reduced fPC1. The direction of the association between connectivity and motor activity was varying between the left and right hemispheres for the hippocampus, parahippocampal regions and for the subgenual ACC.

For the CON, we identified with TFNBS one subnetwork associated with fPC1 scores (all $p_{\text{fwe-corrected}} < 0.0001$). Connectivity between regions of this subnetwork was negatively associated with reduced fPC1 for insular regions, dorsal and mid ACC regions and left infero-parietal cortex. Connectivity was increased bilaterally in fronto-opercular regions and dACC.

For the FPN, we identified with TFNBS one subnetwork associated with fPC1 scores (all $p_{\text{fwe-corrected}} < 0.0001$). Connectivity between regions of this subnetwork was negatively associated with reduced fPC1 for bilateral parietal regions and medial prefrontal region, right polar cortex, DLPFC regions and left precuneus. Connectivity was increased in several left prefrontal regions and in the right precuneus.

A. Associations between brain functional connectivity and reduced fPC1



B. Associations between brain functional connectivity and reduced fPC2

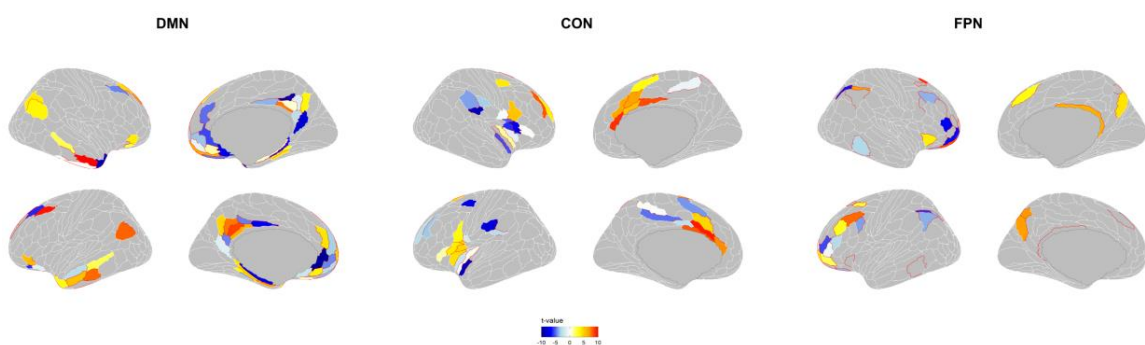


Figure 2. Brain subnetworks associated with reduced scores of principal components of motor activity in late-life depression

A. Brain regions whose connectivity is significantly associated with scores of the functional principal component 1, detected by TFNBS. Estimated Marginal Effects of each ROI are reported to interpret the direction of the association when scores of fPC1 are reduced, i.e., when apathy severity increases. **B.** Brain regions whose connectivity is significantly associated with fPC2 scores detected by TFNBS. Estimated Marginal Effects of each ROI are reported to interpret the direction of the association when scores of fPC2 are reduced, i.e., when apathy severity increases. **Acronyms:** CON: Cingulo-Opercular Network, DCA: 2018 Diagnostic Criteria for Apathy,

1 *DMN: Default-Mode Network, fPC1: first functional principal component, fPC2: second functional principal*
2 *component, FPN: Fronto-Parietal Network.*

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5 ***Association between the second principal component of activity and brain intranetwork functional***
6 ***connectivity activity***
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10 The statistically significant results are reported **Figure 1B** and **Supplementary Table S2**.

11 For the DMN, we identified with TFNBS one subnetwork associated with fPC2 (all $p_{\text{five-corrected}} < 0.0001$).
12 Connectivity between regions of this subnetwork containing bilateral posterior cingulate regions,
13 bilateral parietal regions, medial, bilateral superior temporal sulcus, left temporal pole and right medial
14 polar prefrontal regions was positively associated with reduced fPC2. Connectivity was decreased in
15 bilateral pre-genual ACC regions, bilateral inferior temporal regions, in left polar prefrontal medial
16 regions, left posterior cingulate regions, left hippocampal and parahippocampal regions.
17

18 For the CON, we identified with TFNBS one subnetwork associated with fPC2 scores (all $p_{\text{five-}}$
19 $\text{corrected} < 0.0001$). Connectivity between regions of this subnetwork was positively associated with
20 reduced fPC2 for bilateral dACC, left insular regions and right frontal superior regions. Connectivity
21 was reduced for left dACC, dorsal medial region and antero-lateral regions, right fronto-opercular
22 cortices and inferior parietal lobule.
23

24 For the FPN, we identified with TFNBS one subnetwork associated with fPC2 (all $p_{\text{five-corrected}} < 0.0001$).
25 Connectivity between regions of this subnetwork was positively associated with reduced fPC2 for
26 bilateral precuneus regions and left latero-polar and DLPFC regions. Connectivity was reduced
27 bilaterally in anterior lateral prefrontal regions, superior parietal regions, and right parahippocampal
28 cortex.
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41 **3.4 Association between motor activity and structural connectivity**
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43 We found no significant associations between DTI metrics or NODDI metrics along the selected white-
44 matter tracts and fPC1 or fPC2 of motor activity. Associations between fPC and structural connectivity
45 are reported in **Table 3**.
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Tract	DTI						NODDI									
	Fractional Anisotropy			Mean Diffusivity			Orientation Dispersion Index			Partial Volume						
	Corr. Coef.	Min. cluster size FWE	Nb of clusters > Cluster FWE	Nb of clusters > Cluster uncorrected	Corr. Coef.	Min. cluster size FWE	Nb of clusters > Cluster FWE	Nb of clusters > Cluster uncorrected	Corr. Coef.	Min. cluster size FWE	Nb of clusters > Cluster FWE	Nb of clusters > Cluster uncorrected				
CA	0.51	35	0	2	0.61	58	0	1	0.47	31	0	0	0.54	33	0	0
CC_1	-0.34	35	0	0	0.38	58	0	0	-0.32	31	0	0	-0.25	33	0	0
CC_2	-0.45	35	0	0	0.42	58	0	0	-0.49	31	0	0	0.45	33	0	0
CC_3	-0.33	35	0	0	-0.18	58	0	0	-0.41	31	0	0	-0.38	33	0	0
CC_4	-0.36	35	0	0	0.15	58	0	0	-0.35	31	0	0	0.35	33	0	0
CC_5	-0.28	35	0	0	0.50	58	0	0	-0.30	31	0	0	0.49	33	0	0
CC_6	-0.34	35	0	0	0.30	58	0	0	-0.53	31	0	1	0.36	33	0	0
CC_7	-0.27	35	0	0	-0.38	58	0	0	-0.37	31	0	0	0.39	33	0	0
CG_left	-0.44	35	0	1	0.59	58	0	2	-0.34	31	0	0	0.31	33	0	0
CG_right	-0.37	35	0	0	0.43	58	0	1	-0.36	31	0	0	0.24	33	0	0
CST_left	-0.34	35	0	0	0.47	58	0	0	-0.37	31	0	0	0.43	33	0	0
CST_right	-0.33	35	0	0	0.32	58	0	0	0.29	31	0	0	0.41	33	0	0

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21	ILF_left	-0.31	35	0	0	0.29	58	0	0	-0.34	31	0	0	0.30	33	0	0
22	ILF_left	-0.31	35	0	0	0.29	58	0	0	-0.34	31	0	0	0.30	33	0	0
23	ILF_fight	-0.35	35	0	0	0.44	58	0	0	-0.45	31	0	0	0.38	33	0	0
24	ILF_fight	-0.35	35	0	0	0.44	58	0	0	-0.45	31	0	0	0.38	33	0	0
25	SLF_I_left	-0.29	35	0	0	0.49	58	0	1	-0.35	31	0	0	0.35	33	0	0
26	SLF_I_left	-0.29	35	0	0	0.49	58	0	1	-0.35	31	0	0	0.35	33	0	0
27	SLF_I_right	-0.32	35	0	0	0.31	58	0	0	-0.40	31	0	0	0.35	33	0	0
28	SLF_I_right	-0.32	35	0	0	0.31	58	0	0	-0.40	31	0	0	0.35	33	0	0
29	SLF_II_left	-0.30	35	0	0	0.39	58	0	0	0.32	31	0	0	0.42	33	0	0
30	SLF_II_left	-0.30	35	0	0	0.39	58	0	0	0.32	31	0	0	0.42	33	0	0
31	SLF_II_right	-0.40	35	0	0	0.39	58	0	0	-0.31	31	0	0	0.27	33	0	0
32	SLF_II_right	-0.40	35	0	0	0.39	58	0	0	-0.31	31	0	0	0.27	33	0	0
33	SLF_III_left	-0.52	35	0	0	0.39	58	0	0	0.36	31	0	0	0.39	33	0	0
34	SLF_III_left	-0.52	35	0	0	0.39	58	0	0	0.36	31	0	0	0.39	33	0	0
35	SLF_III_right	-0.45	35	0	0	0.36	58	0	0	-0.30	31	0	0	0.30	33	0	0
36	SLF_III_right	-0.45	35	0	0	0.36	58	0	0	-0.30	31	0	0	0.30	33	0	0
37	UF_left	-0.38	35	0	0	0.22	58	0	0	-0.41	31	0	0	-0.33	33	0	0
38	UF_left	-0.38	35	0	0	0.22	58	0	0	-0.41	31	0	0	-0.33	33	0	0
39	UF_right	-0.34	35	0	0	0.31	58	0	0	-0.39	31	0	0	0.32	33	0	0
40	UF_right	-0.34	35	0	0	0.31	58	0	0	-0.39	31	0	0	0.32	33	0	0
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Table 3. Associations between diffusion MRI metrics and first principal component of motor activity by tract

Along each white matter tract, significant clusters of metrics associated with *f*PC1 had to be greater than the familywise error rate cluster size, for a *p*-value of 0.05. We reported the number of significant clusters without the adjustment for multiple comparisons for the number of tracts (an adjustment is performed for 100 points along the tracts). **Acronyms:** DTI: Diffusion Tensor Imaging, Corr. Coef: Pearson correlation coefficient, *f*PC1: first principal component scores of motor activity, FWE: Family-wise error, Min. cluster size FWE: Minimum cluster size after FWE-correction, NODDI: Neurite Orientation Dispersion and Density Imaging, Nb of Clusters > Cluster FWE: number of significant clusters after family-wise error correction on the number of points and tracts, Nb of Clusters > Cluster uncorrected: number of significant clusters without the adjustment for multiple comparisons for the number of tracts

4. Discussion

We investigated the interplay between apathy, actimetry and MRI-derived functional and structural connectivity in LLD. Our primary findings are that the two first fPC of motor activity were significantly associated with apathy, namely, a reduced overall activity and a late chronotype. Reduced motor activity was associated with reduced connectivity within the default-mode, the cingulo-opercular and the frontoparietal networks, while late chronotype was associated with more heterogenous connectivity between both hemispheres in the same regions. We did not find significant associations between microstructural metrics of white matter and patterns of motor activity. Taken together, these innovative results suggest that motor activity patterns and their associated functional neural connectivity play a pivotal role in understanding the complex interplay between apathy and LLD.

Patterns of Motor Activity are Associated with Apathy

We found that apathy severity was associated with reduced mean activity while a social apathy was associated with a late chronotype in LLD. The two patterns of activity were robustly found in general adult population (44,45) notably in elderlies (13,46), as well as in bipolar depression (47) and Alzheimer's disease (11). The association between reduced mean activity, apathy severity and functional impairment supports earlier studies that have linked decreased average activity to apathy in Alzheimer's disease (11), poor health (44), reduced social activity and increased depression symptoms in general population (45) and bipolar disorder (47). Mean activity was also predictive of dysexecutive function (13) and mortality (13,46) in elderly population, confirming its potential predictive utility in LLD. The late-morning and late-sleep pattern of activity suggests having captured individuals chronotypes (48), confirming the association between late chronotype and psychiatric disorders (49). In depression, late-chronotype has been associated with elevated depression severity (50,51), cognitive complaints (52) and risks of depressive episodes (53), putatively by a deficit of emotion regulation (54,55). Our results suggest that social apathy, measured by AMI, might be related to late-chronotype, corroborating reported associations between late-chronotype and reduced social activity in general population (44) and depression severity in mood disorder (47). However, studies found that early-chronotype was associated with informant-rated scores of apathy in Alzheimer's disease (11) or cognitive decline in older adults at risk of dementia (12,13). As the AMI is a self-rated questionnaire, lower scores might be associated with higher self-recognition of social impairment induced by depression than by cognitive deficits.

Within RSN Connectivity Associated with Mean Diurnal Motor Activity

We found that mean motor activity was associated with increased rsFC within the DMN, the CON and the FPN in LDD.

1 The DMN is central in depression pathogenesis (55,56). Sedentary motor behavior is correlated with
2 reduced connectivity of the DMN in elderlies (58) and in adults (59), notably between ventromedial
3 regions of the DMN (53). Volumes of the hippocampus and para-hippocampal regions were also found
4 associated with physical activity in healthy elderlies (60–62) and vascular mild-cognitive impairment
5 (63). Hence, sedentarity, as a consequence of apathy, might be a maintenance factor of depression and
6 a risk factor of dementia (3,7) by strengthening dysfunctions of the DMN associated with LLD.
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9 The CON was positively associated with mean activity, confirming previous findings in elderlies (58).
10 More specifically, increased connectivity between dACC, anterior insula and supplementary motor area
11 were predictive of sedentary behaviors in elderly population (64). However, key regions implied in
12 motor cognitive control showed a negative association with mean activity; namely dACC regions and
13 bilateral fronto-opercular cortex. While one seed-based study found a positive association between
14 dACC and motor activity in vascular mild-cognitive impairment (65), the choice of the seed might have
15 limited the detection of heterogenous effect across dACC subregions contrary to the Glasser’s atlas (30).
16 Regarding the FPN, we found a global positive association between rsFC and mean motor activity, and
17 a reduced rsFC in the left DLPFC, as reported in healthy elderlies (66,67). These regions are involved
18 in motor planning and cognitive control (68,69), with their activation during executive function task
19 moderated by subjects’ physical activity in elderlies. Mean motor activity might thus measures indirectly
20 dysexecutive syndrome, sharing apathy pejorative course in LLD (70) and supposed central in LLD
21 development (71).
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32 **Within-RSN Connectivity Associated with Diurnal Chronotype**

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34 Diurnal chronotype was associated with heterogenous rsFC between the left and right hemispheres in
35 LLD, compared to fPC1. DMN activity correlates with late chronotype in healthy adults with higher
36 connectivity between the precuneus and medial prefrontal cortex (72), while a reduced connectivity
37 between the posterior DMN (73) and the amygdala was found mediating the association between late
38 chronotype and depression symptoms (74). Abnormal expression of genes regulating chronotypes had
39 been reported in the ACC, the hippocampus and the DLPFC in depression (74), suggesting that
40 dysregulation of circadian rhythm is central in depression pathogenesis by disrupting DMN
41 connectivity.
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49 Regarding the CON, we found that late-chronotype subjects had increased rsFC the bilateral dACC, and
50 modified connectivity between the insula, supramarginal gyrus and supplementary motor areas. This
51 confirms studies in healthy subjects finding modified rsFC between the ACC and insula, or between the
52 ACC and right superior frontal gyrus extending to the supplementary motor area between chronotypes
53 (75). In depression, late chronotype has been associated with impaired functional activity of the
54 supramarginal cortex and superior orbitofrontal regions (76), and reduced rsFC between the dACC and
55 the amygdala (78). These changes in CON connectivity related to chronotype might be indicative of the
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1 modulating effect of circadian rhythm on reward processing (79) in apathy in LLD, as reduced dACC
2 activity was reported in late chronotype participants during monetary reward paradigm (80,81).

3 For the FPN, we found an association between late chronotype and the DLPFC, precuneus and superior
4 parietal cortex connectivity. The rsFC between the DLPFC and the cuneus has been found to mediate
5 the impact of social jetlag on subclinical depressive symptoms in adults (82). In depression, genetic
6 studies reported reduced expression of circadian regulating genes in the DLPFC compared to healthy
7 controls (74,82) which corroborates the potential utility of this region as a brain marker of depression
8 vulnerability. With the DMN, modified connectivity in the FPN might be partly closely related to
9 circadian rhythm dysregulation yielding to depression severity.
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16 **Absence of Association between Patterns of Motor Activity and White-Matter** 17 **Connectivity** 18 19

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21 We found no significant association between DTI and NODDI metrics and motor activity patterns. This
22 result deceives our expectation with respect to the findings on white matter lesions in LLD (84,85). DTI
23 studies in elderlies found correlation between global FA and physical activity (87,88,89), as well as
24 between physical activity and FA in the body of the corpus callosum or temporal areas (33,88). In
25 younger adults, FA levels in the genu and body of the corpus callosum was associated with physical
26 activity in bipolar disorder (90) and moderated the association between physical activity and spatial
27 working memory (91). Association between activity level and mean diffusion kurtosis in the inferior
28 longitudinal fasciculus and fronto-occipital was also reported in schizophrenia (92). All these studies
29 combined tensor diffusion metrics with tract-based spatial statistics (93). While this method provides
30 statistical power, they may suffer from high false positive rate notably in regions of crossing pathways
31 such as the corpus callosum (94). The multi-compartment model we used is meant to identify more
32 precisely these tracts (95). Similarly, the cluster-wise statistical method we used is more stringent than
33 the global brain or tract-specific metrics computed in the aforementioned studies.
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45 **Limitations** 46

47 Several limitations should be considered.

48 Our study employs a cross-sectional design with a recording period of three days. While being the
49 minimal period for acceptable estimation of motor activity (96,97), this short period may have prevented
50 us describing more robust assessment of participants activity. We tried to circumvent this by estimating
51 individual trajectories, but the models' predictions can have reduced variability in the results.
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54 Moreover, PCA is subject to high variance and might not be exactly replicable across cohorts. The top
55 two fPC are nevertheless stable across studies (11-12, 42-45) which can be explained by the fact that
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1 fPC1 summarizes the maximum of the total variance, *i.e.* the mean, while fPC2 is often related to the
2 rate of change of motor activity over time.

3 Furthermore, our sample size was relatively small, which may limit the generalizability of our results,
4 in particular concerning the unapathetic sample which only contained 11 subjects. Further studies with
5 stratification on the apathetic group could improve the exploration of the utility of actimetry to evaluate
6 functional impairment.
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10 11 12 13 **5. Conclusion** 14

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16 Our results provide new insights of the cerebral basis of apathy-related pattern of actimetry in LLD. We
17 show that these markers are more strongly associated with functional connectivity changes than
18 measures of low-grade inflammation of white matter tracts. These results suggest that actimetry might
19 better subserve the goal of treatment effect monitoring, active on brain functional connectivity, than a
20 marker of cognitive decline. Improvement in recruiting patients with LLD without criteria for significant
21 apathy might increase between-group differences especially for detecting microstructural white-matter
22 lesions.
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30 **AUTHORS' CONTRIBUTIONS**

31 JCR: Formal analysis; Methodology; Software; Visualization; Writing - original draft.

32 TD: Data curation; Investigation

33 RH: Formal analysis; Methodology; Software.

34 SD: Methodology; Software.

35 IMG: Data curation.

36 WL: Data curation.

37 EB: Resources; Writing - review & editing.

38 LB: Resources; Writing - review & editing.

39 DD: Resources; Investigation.

40 JMB: Resources; Investigation; Writing - review & editing.

41 RD: Investigation; Funding acquisition.

42 JC: Conceptualization; Methodology; Resources; Software; Supervision; Validation; Writing - review
43 & editing.

44 GR: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Resources;
45 Supervision; Validation; Writing - review & editing.

46 All authors read and approved the final manuscript.
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CONFLICTS OF INTEREST

None

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Part V
General Discussion

Chapter 10

General Discussion

OVERVIEW

We provide a summary of the main results of our studies, before discussing their limitations and the perspectives. We found that apathy evaluations shared modifications of functional connectivity in the DMN and in the FPN, reflecting reduced emotion regulation and dysexecutive function. We found two motor activity patterns associated with apathy in late-life depression: a reduced overall diurnal activity and a late-chronotype pattern. We argue that reduced overall activity is linked to apathy severity and risk of dementia while late-chronotype is more specific to social apathy in depression. The limitation of the study pertains to the small sample size, the cross-sectional design and short recording period limit the assessment of activity patterns, the inclusion of both late-onset and early-onset depressed individuals, as well as the caution in interpreting intranetwork resting-state functional connectivity. We discuss how future perspective, combining multimodal brain imaging, multimodal behavioral recordings could help to improve current models of apathy in LLD for better diagnosis and monitoring.

10.1 Main Results

- **Do apathy evaluations measure the same pathological phenomenon?**

Our results suggest that apathy evaluations measure shared modifications of functional connectivity with some specificities between the scales.

Regarding the regions in common, apathy evaluations were all associated with reduced connectivity between the pregenual ACC and precuneus regions in the DMN, as well as increased connectivity between DLPFC regions and between dorsal ACC regions in the FPN. This suggests that apathy measures commonly capture processes related to reduced emotion regulation, stimulus valuation and dysexecutive function. Interestingly, while anhedonia and dysexecutive function are classically excluded from definition of apathy (Dickson & Husain, 2022; Marin, 1991), they might be captured by the different apathy scales.

The AES tended to measure more specifically reduced intranetwork connectivity in the ventromedial regions of the DMN, suggesting a more specific measure of dysfunction in emotion regulation, context valuation and self-awareness. AES was also associated with reduced intranetwork connectivity in the goal-directed behavior network from pregenual to dorsal ACC regions. This suggest that apathy severity in LLD might be related to impaired processing of stimulus value during decision-making context. On the other hand, higher AMI scores were associated with increased intranetwork connectivity in the frontoparietal network. This suggests that social apathy in LLD might be underpinned by dysexecutive functions such as decision-making, conflict resolution, and language recognition, all implied in social behaviors. The DCA showed mixed associations with rsFC in the DMN and FPN, without a clear pattern. This may mean that functional impairment associated with apathy may emerge from heterogeneous processes in resting-state networks. The absence of association of DCA with the CON can suggest that the anterior insula might not be the main factor implicated in clinical state of apathy; i.e. cause functional impairment, contrary to previous results which classified apathy based on AES scores (Yuen et al., 2014).

- **How do patterns of motor activity relate to apathy in LLD?**

Motor activity assessment provides an objective and ecological means of examining the behavioral manifestations of apathy in depression. We identified two primary patterns of motor activity associated with apathy in LLD: reduced overall diurnal motor activity and a late-chronotype pattern, characterized by late-morningness and late-sleep.

Reduced overall activity was associated with apathy severity measured by AES and tended to be associated with functional impairment due to apathy. This result confirms previous findings relating this pattern of motor activity to apathy severity, predictive of executive dysfunction, risk of dementia (David et al., 2012; Zeitzer et al., 2013, 2018), depression relapses in bipolar disorders (Gershon et al., 2016) and even mortality in older adults (Zeitzer et al., 2018). This suggests that reduced mean diurnal activity could be a prognostic factor of severe depression and risk of dementia in LLD.

Concerning the late-morning and late-sleep pattern of activity, we interpret it as having captured individuals chronotypes. The late-chronotype was associated with AMI suggesting that this pattern is more specifically an expression of social apathy, confirming previous studies in general population, finding reduced social activity in late-chronotype individuals. Late-chronotype have been robustly associated with an increased risk of psychiatric disorders, notably depression (Kivelä et al., 2018), while early-chronotype was more associated with apathy in Alzheimer's disease (Zeitzer et al., 2013) or with cognitive decline in older adults at risk of dementia (Alfini et al., 2021; Zeitzer et al., 2018). Taken together, the reduced engagement in daytime activities, which is a cardinal symptom of depression (American Psychiatric Association & American Psychiatric Association, 2013), as well as its association with depression but not with dementia, suggest that late-chronotype might be a behavioral marker of depression severity in LLD more than cognitive impairment.

In summary, each apathy scale exhibits distinct patterns of association with motor activity and functional neural connectivity, suggesting that they measure different mechanisms participating in reduced goal-directed behavior in LLD. AES primarily focuses on reduced overall motor activity and is linked to disruptions in the DMN and GBN. AMI, on the other hand, was associated with chronotype preference, particularly late-morningness and late-sleep patterns, and increased connectivity within the FPN. DCA shows some associations with both motor activity and functional connectivity but lacks a clear trend. These differences highlight the multifaceted nature of apathy and the need for multiple assessments to comprehensively capture its various dimensions and mechanisms.

- **Dysfunction of goal-directed behaviors and LLD pathogenesis**

Our work provides evidence on how the assessment of motor activity contributes to our understanding of the triple link between goal-directed behaviors, apathy and depression pathophysiology. Our results advocate for multiple mechanisms associated with depression development and at stake in LLD apathy. The anomalous brain connectivity in the DMN and CON, constantly associated with apathy evaluation scales and motor patterns, suggests that apathy in LLD could arise from emotional dysregulation. The abnormal functional connectivity within pregenual ACC regions could explain a loss of goal-directed behaviors due to an impaired stimulus valuation and emotion regulation in LLD (Husain & Roiser, 2018; Price & Drevets, 2012). In the CON, the insula and dorsal ACC are involved in emotional reactivity, particularly in fear conditioning (Alvarez et al., 2011). We found that CON connectivity was more specifically associated with social apathy, which suggest an impaired emotional salience in social contexts. As pregenual ACC regions are believed to provide afferent information to dorsal ACC on stimuli values (Le Heron et al., 2018; Pessiglione et al., 2018), the decoupling we observed between these regions within the goal-oriented behavior network may indicates a dysregulation in the ability to

process stimuli, adapt to new situations and execute behavior. Thus, emotion dysregulation might translate behaviorally in reduced diurnal activity and late-chronotype profiles in patients.

Another important finding, related to emotion regulation, is that the late-chronotype seems more specific to depression-related apathy. Indeed, late-chronotype was significantly associated with social apathy as well as with a modified resting-state networks connectivity of all the networks, notably the bilateral insula sub-regions of the CON, in comparison to mean diurnal activity. Interestingly, previous studies have reported that the association between this late-chronotype and subclinical depression symptoms was mediated by modified functional connectivity between DLPFC regions as well as between PCC and precuneus within the DMN (Jia et al., 2023), while decrease performance in reward processing was associated with reduced activity of dorsal ACC regions in late-chronotype individuals (Byrne et al., 2019; Hasler & Clark, 2013). It has been shown that these regions, as well as key limbic regions such as the hippocampus, were the locus of abnormal expression of genes regulating these chronotypes in depression (Edgar & McClung, 2013; J. Z. Li et al., 2013). However, the relationship between chronotype and depression is complex, involving biological, psychological and social factors (Zou et al., 2022), and multidirectional as impaired circadian rhythm can worsen depressive symptoms, adding mental fatigue, loss of energy and failures in diurnal activity, but can also be caused other depressive symptoms such as ruminations or social isolation. Thus, the deregulation of circadian rhythm could be a potential process participating in social apathy in LLD, being associated with modified connectivity of CON brain regions involved in reward processing in social context, as well as explaining symptom severity by disrupted emotion regulation.

Our results also go in pair with the dysexecutive syndrome hypothesis of LLD (Alexopoulos, 2001). Executive dysfunctions are frequent in LLD, persisting during remission (Butters et al., 2004; Diniz et al., 2013) and correlating with disability as well as apathy. The dysexecutive syndrome hypothesis postulates that this subtype of depression is predictive of a worse depression course, associated with apathy. We found that apathetic patients had impaired cognitive control in comparison to non-apathetic LLD. Also, apathy severity, social apathy and functional impairment were associated with reduced functional connectivity in the FPN, crucial for executive functions such as decision-making and cognitive control. These changes in the FPN may contribute to the cognitive and emotional impairments observed in depression.

- **Dysfunction of goal-directed behaviors and LLD prognosis**

Our findings also help to understand the relationship between apathy and poor LLD prognosis, namely, treatment-resistant depression and risk of dementia.

We identified several regions with modified connectivity associated with apathy which have been involved in antidepressant resistance. In the DMN, modifications in resting-state connectivity in pregenual ACC and ventromedial regions had been reported in treatment resistant depression (Mayberg et al., 2005; Price & Drevets, 2012). More specifically, the subgenual ACC region (Brodmann area 25), is a key region for both processing of experienced pleasure and antidepressant response (Pizzagalli, 2011) which could explain the link between apathy and treatment resistance. Similarly, we found modified intranetwork rsFC in the FPN and the CON involving regions such as the insula, the DLPFC and the mid-cingulate cortex. Modified connectivity between these regions have been reported to mediate the association between presence of apathy and poor antidepressant response in LLD (Aizenstein et al., 2014; Karim et al., 2017; Oberlin, Respino, et al., 2022). Such mechanism could link dysexecutive function, apathy and antidepressant treatment resistance, as reported in depression (Pimontel et al., 2012, 2016; Vancappel et al., 2021).

Another important result from our study pertains to the link between apathy in LLD and dementia. First, all apathy evaluations were associated with reduced connectivity between the pregenual ACC, dorsal ACC and precuneus regions in the DMN, as well as increased connectivity between DLPFC regions in

the FPN. Thus, we found modified connectivity in the same regions than those describe in neurodegenerative disorders (Le Heron et al., 2018), which aligns with the view of apathy as a transdiagnostic entity (Husain & Roiser, 2018). Noteworthy, by studying internetwork rsFC between medial frontal regions implied in goal-directed behaviors, we found a subnetwork with a decreased connectivity between anterior prefrontal regions and an increased connectivity with dorsal ACC posterior regions. This reverse coupling between anterior and posterior prefrontal regions could be explained by the anterior-posterior gradient of cerebral blood flow observed in LLD (Abi Zeid Daou et al., 2018), and strengthening the neurovascular hypothesis (Alexopoulos, 2019). Behaviorally, reduced mean diurnal motor activity, associated with apathy severity and functional impairment, was correlated with modified connectivity in the same regions. As mean diurnal activity is predictive of dysexecutive function and dementia (Zeitzer et al., 2018), the modified connectivity we found might also be early manifestations of dementia, explaining the link between apathy and risk of dementia. Conversely, the absence of a significant association between patterns of motor activity and white-matter connectivity pleads for an absence of lesions in this network. This result deceives our initial expectation compared to the large literature reporting on white matter lesions in LLD. In LLD, reduced FA have been found in tracts supporting goal-directed behaviors such as the corpus callosum, or the uncinate fasciculus (Hollocks et al., 2015). In healthy older adults, FA in the body of the corpus callosum has been associated with mean physical activity (Kim et al., 2020; Burzynska et al., 2017; Verkooijen et al., 2017). The discrepancy in the results might be due to the divergence the techniques used. All previous studies measured white matter using tensor diffusion metrics and tract-based spatial statistics which is a sensitive technique but with a high risk of bias in regions where pathways of different tracts merge such as the corpus callosum (Bach et al., 2014). The multi-compartment model we used is meant to overcome these limits by a more precise identification of the tracts (Kamiya et al., 2020). Moreover, we might have used a too stringent method by identifying cluster of reduced metrics along a track, compared to the global brain or tract-specific metrics computed in the aforementioned studies.

10.2 Limitations of the thesis

This study provides valuable insights into the relationship between motor activity patterns, resting-state functional connectivity and apathy in LLD. However, it is essential to acknowledge several limitations that impact the interpretation of our findings.

- **Defining apathy as goal-directed behavior**

The interpretation of apathy we made has to be taken with caution. Results from the AMI can be ambiguous as it is the only self-assessment scale of apathy. We interpret the results with respect to the social dimension of apathy, but low self-esteem, as described in depression, could also influence the results. However, controlling for depression severity in connectivity analysis did not change our results (**Appendix 1**), suggesting that our results were more specific to social apathy. Regarding functional impairment associated with apathy, as assessed by the DCA, the study has a relatively small design, including only 11 participants which may have affected our results. Consequently, the higher proportion of apathetic participants has potentially reduced the ability to detect rsFC components specifically associated with apathy diagnosis in the CON.

A related issue concerns our choice of recognizing multiple dimensions of apathy (Dickson & Roiser, 2022), following current definitions of apathy as impaired goal-directed behavior (P. Robert et al., 2018). It can be argued that integrating multiple dimensions to apathy such as emotional processing or executive functioning may blur the boundaries of apathy instead of providing a unifying account of this construct. However, the deconstruction of apathy into components, as done in the goal-directed behavior model, can be understood as a transient step in a scientific effort to identify the functions

impaired in apathy as well as their modified organization specific to neurological and psychiatric diseases. This perspective matches the research domain criteria framework (Insel et al., 2010), in its intention to study the cerebral bases of psychiatric diseases from dysfunctions of biologically-founded psychological systems. By doing so, the goal-directed behavior model provides a framework to synthesize and organize a large amount of data to explain apathy in specific disorders, more than an unspecific definition of apathy.

- **Interpreting accelerometry data**

Another point to underline is relative to the interpretation of accelerometry data.

While accelerometry provides an objective measure of ambulatory activity, the proportion of goal-directed behavior capture is not clearly defined. Studying principal components of motor activity enables to reduce complex behavior to styles of activity, associated with generic biological systems such as circadian rhythm. Thus, correlating components of motor activity with apathy scores as we did, provides an indirect measure of goal-directed behavior which may gain to be completed by qualitative analysis (Littner et al., 2003).

Moreover, our study employed a cross-sectional design with a relatively short recording period of three days. While this duration is acceptable for estimating motor activity (Sasaki et al., 2018), the assessment of activity patterns might be limited, particularly in response to contingent events. Longitudinal design with longer periods of recording could enable to observe the dynamics relationship between motor activity, poor clinical course and brain dysconnectivity with more robustness as well as determine the predictive utility of accelerometer data.

Finally, the principal components of motor activity depend on the dataset and may not be easily replicable across different cohorts. We tried to mitigate this limitation by estimating individual trajectories from optimal model selection. In addition, we found patterns of activity robustly reported in the literature.

- **Interpreting resting-state functional connectivity**

The meaning of the intranetwork rsFC results also has to be interpreted with care.

The TFNBS method enables a powerful identification of regions associated with apathy scores or motor activity but do not provide a measure of the direction of the association. Via estimated marginal means, we reported the average connectivity of a region with all the regions in this subnetwork, for descriptive purpose. Thus, a same region may have its connectivity associated differently with motor activity across regions of the subnetwork.

Also, the Glasser atlas is a precise brain parcellation which can show heterogeneous associations between connectivity and apathy or motor activity within a same brain area. For instance, the dorsal ACC comprises 11 regions, which can render difficult its simple interpretation in terms of increase or reduction of activity. While we discussed the general tendencies within the resting-state networks, we did not delve into the complexity in terms of mechanisms.

Furthermore, we regressed out the global signal to obtain sparse correlation matrices. This implies that the changes in connectivity we found are relative to the global signal, removing a part of neural activity.

- **Specificity of apathy in LLD**

Finally, by only complying to the definition of LLD to recruit participants, *i.e.* the presence of a major depressive disorder after 60 year old, we have mixed late-onset depressed individuals with aged early-onset depressed individuals. Twenty participants had the criteria for early-onset LLD, among which 13

had their first depressive episode before 50 years old. Thus, the mechanisms underlying apathy might differ in our sample, between a pejorative evolution of the symptoms in individuals suffering from chronic depression, and the apparition of a new depression with severe features in late-onset depression. As a consequence, we cannot conclude if the results of the thesis are specific to LLD and could not be found in younger populations. This assertion is strengthened by the fact that we did not find white matter microstructural modifications associated with apathy, evocative of vascular lesions as reported in LLD. We planned further analyses, comprising a study of cerebral perfusion and combined microstructural metrics, which could help to better characterize patients' brain vascular status and provide evidence towards the vascular depression hypothesis.

10.3 Perspectives

We would like to finish this discussion by contextualizing this thesis within neurosciences and further developments needed for research on apathy in LLD.

- **Developing biomarkers of apathy**

Our study provides evidence for a statistical association between specific patterns of motor activity, functional brain connectivity and apathy in LLD. This represents a first step in the evaluation of motor activity performance for apathy assessment which would need further evaluations for clinical utility (Pletcher & Pignone, 2011). One such performance to evaluate is the diagnosis value of accelerometric data. The use of actigraphy would enable an easy and continuous assessment of an individual's apathetic tendencies in their natural environment. While principal components of motor activity might help to interpret physiological activity patterns associated with apathy, many features of activity can be used for diagnosis purposes. A collaborative work with our team has found promising results from the same sample of participants. We showed that duration of inactivity, activity and walking periods, as well as their spectral decomposition, over 72 hours of recordings, were able to discriminate LLD from healthy controls with an accuracy of 100%, as well as apathetic from non-apathetic with a accuracy of 93% (Vianne et al., 2023). To determine the predictive utility of activity features on cognitive performance or depression course, longitudinal studies in LLD should be performed.

Another important development would be to validate the pathophysiological models of apathy in LLD, via combining multiple imaging modalities. The neurovascular hypothesis of LLD addresses many possible dysfunctions in cerebrovascular coupling associated with ageing. Such dysfunctions comprise cerebral blood perfusion at rest, cerebrovascular reactivity or cerebral autoregulation which can impact fMRI signal (Tsvetanov et al., 2020). We plan to study brain pulsatility (Desmidt et al., 2017) on the same sample of LLD. This technique is sensitive to detect microvascular changes, notably in depression where it shows impaired blood perfusion not found with conventional markers of brain perfusion such as white-matter hyperintensities. Regarding neuroinflammation hypothesis, quantitative magnetic transfer is a promising technique to measure subtle structural lesions in LLD. A recent study in depression have found that peripheral inflammation was associated with modified proton density in key DMN nodes and a reduced hubness in terms of rsFC (Kitzbichler et al., 2021). PET imaging is also a promising technique to selectively study impaired neural systems specific to a class of radioligands. In depression, PET imaging have provided consistent results of elevated TSPO, a neurobiomarker of inflammation (Meyer et al., 2020). The combination of techniques could greatly help to test and improve current neural models of apathy in LLD as well as their association with dementia.

- **Towards ecological neurosciences**

Our study joins the recent efforts made to apply ecological tools to explore behavior in its real-world complexity. Behavior has been defined “*as the macroscopic expression of neural activity, implemented by muscular and glandular contractions acting on the body, and resulting in egocentric and allocentric changes in an organized temporal sequence*” (Gomez-Marín et al., 2014). Behavior thus spans a wide range of activities such as speech, writing, locomotion, facial expressions, building construction or meditation. Three main characteristics were recognized to behavior as being relational, dynamic and high dimensional. Being relational implies the need to specify the context in which the behavioral phenomenon is defined. Dynamics of behavior refer to the fact that behaviors are inherently sequence of actions meant to adapt to a changing environment. High dimensionality means that behavior appears complex and variable, such as when someone walk while talking to her mobile phone. While popular in animal neuroscience or sociology, the development of ethology in human neuroscience, particularly in psychiatry, is new and promising for a comprehensive measurement of symptoms, bridging different levels of analysis of mental disorders and to promote join neuroscience research to clinical practice.

One main benefit of ethology is to provide a direct and faithful measure of behavior. Digital-health is promising to assess the social dimension of apathy. The attitude and behavior of individuals towards digital application reflect social activity via communication or interest in social media. The term “ecological momentary assessment” (Shiffman et al., 2008) has been coined to designate these evaluations are well-used repeated, real-time assessments of phenomena (like cognitions, emotions and behaviors) over a period of time in naturalistic settings. The combined use of ambulatory evaluation and semi-natural settings also provides a comprehensive assessment of behaviors. For instance, the program ECCOCAPTURE (Godefroy et al., 2021) comprises an ethological evaluation of apathetic patients in a semi-natural laboratory and an ambulatory evaluation of patients’ behaviors via remote monitoring by actimetry. measuring motor activity, skin conductance and heart rate. The semi-natural laboratory provides a detailed descriptions of behavior patterns components (ethograms) in order to determine the whole behavioral repertoire related to apathy which could be into linked to more experimental psychological measures. The ambulatory evaluation of patients’ behaviors via actimetric monitoring measures motor activity together with physiological marker of emotions such as skin conductance and heart rate. Importantly, this program takes into consideration the relational aspect of behavior by requiring the active participation of caregivers in this research program.

This program aligns with current proposals in translational psychiatry (Shemesh & Chen, 2023) and animal neurosciences (Gomez-Marín et al., 2014) to include ethological methods to bridge complementary levels of analysis of behavior. Semi-natural setups provide realistic settings to measure reactions to stressors and help to better distinguish behavioral expression of fear, from anticipatory anxiety or panic reactions (Perusini & Fanselow, 2015). Such settings follow recent progresses in cognitive psychology on goal-directed behavior. For instance, Huys & Browning (2022) describe modern computational models of motivation applicable to anhedonia. Among these models, the drive-reduction theories of motivation hypothesize that the reward experienced following an event is a function of the degree to which the event moves you towards a homeostatic “set point”. Hence, an agent current state can be defined as his position in a multi-dimensional “drive space”, wherein each distinct dimension can represent different basic drives (a thirst of “x” and a hunger of “y”), and includes a homeostatic set-point, the point at which all the agent’s drives are fulfilled (Keramati & Gutkin, 2014). The aim of the agent being to reach the set point, each reduction of distance to this point triggers reward experienced in the agent. Interestingly, this model incorporates multiple dimensions in the drives of the individual and can be applied to more abstract goals, such as maintaining social status, thus providing a mean to measure complex behaviors as well as their impairment in anhedonia (Huys & Browning, 2022). Moreover, models of decision theory considering effort (Niv et al., 2007) have proven that apathy in depression was related to an increased sensitivity to effort cost but an intact sensitivity to action

outcomes (Vinckier et al., 2022). Taking into consideration the living context where the agent makes these decisions could help to estimate more precisely the parameters of such models.

The promotion of ecological research, based on the comprehensive evaluation of ambulatory behaviors, can also strengthen ambulatory care in psychiatry practice. First, the material equipment and team organization required to perform ecological research are precious elements for an improved follow-up of the patients. Discovering the potential use of these new tools, as well as their meaning in terms of prognosis, could help to develop adaptive programs of ambulatory care and reduce hospitalizations for ambulatory care-sensitive conditions (Freund et al., 2013; Yoon et al., 2012). From these tools, the patient can also learn to recognize his current state and be more participative in his care. The integration of caregivers in the follow-up is a mean to receive feedback on the clinical state of the patient but also on their current attitude towards the medical care services (use of ambulatory service and adaptation of monitoring). Moreover, the combination of ecological research with psychiatric expertise and neuroscientific investigation should help to better understand psychiatric vulnerability to the environment. Measuring and explaining anomalous behaviors of patients in their contexts can help to better identify the social, interpersonal, climatic or urban determinants of psychiatric disorders (Schumann et al., 2023). The findings from this research could support the development of public health programs and facilitate the collaboration between psychiatry and social services.

10.4 Conclusion

To conclude, this thesis suggests that apathy evaluations as well as motor activity are associated with modifications of functional connectivity in subnetworks associated with emotion regulation and dysexecutive function. We found that reduced diurnal activity is linked to apathy severity and may be more specific to risk of dementia, while late-chronotype is more specific to social apathy in LLD. However, the evidence we provide for these interpretations are indirect, limited by the cross-sectional design of the study and the use of resting-state connectivity. Future research, combining multimodal brain imaging, multimodal behavioral recording and longitudinal studies, could help to improve current models of apathy in LLD and validate features of interest for diagnosis.

APPENDIX

SUPPLEMENTARY MATERIAL STUDY 1

1. Supplementary Methods

1.1 Evaluation of apathy

1.2 Connectivity analyses adding the MADRS score as covariate

2. Supplementary Results

2.1 Disconnected brain subnetworks between late-life depression and healthy controls

2.2 Assessment of heterogeneity in detected subnetworks between apathy scales

Supplementary Tables

Table S1. TFNBS identified subnetworks associated with apathy in the depression group

Table S2. Details of the subnetworks identified by TFNBS for each apathy scale.

We remove this table from the thesis for space.

Table S3. Proportion of shared and different components identified by TFNBS between apathy scale

Table S4. Proportion of shared components identified by TFNBS with and without modified MADRS as covariate

Supplementary Figures

Fig S1. Quality control of fMRI data

Fig S2. Subnetworks associated with late-life depression

Fig S3. Subnetworks associated with apathy for each apathy scale

Fig S4. Subnetworks associated with apathy adding the modified MADRS as covariate

1. Supplementary Methods

1.1 Evaluation of apathy

Apathy was assessed by a trained old-age psychiatrist using three scales.

The clinician-rated version of the Apathy Evaluation Scale, is a semi-structured interview which evaluates apathy from the patient's reported interests, activities and daily routine during the four last weeks. This scale consists of 18 items, each item being scored on a 4-point Likert scale. The items evaluate the cognitive, behavior or emotional dimension of apathy. The total score ranges from 18 to 72, with higher scores indicating more apathy. The AES is only validated from its total score¹, as a continuous scale, while the use of a threshold for classifying patients performs modestly².

The Apathy Motivation Index is an 18-item self-report questionnaire which assesses apathy in terms of Behavioral Activation (tendency to self-initiate goal-directed behavior), Emotional Sensitivity (affective responses) and Social Motivation (level of engagement in social interactions). It uses a 5-point Likert scale with higher scores indicating more severe apathy.

The Apathy Diagnostic Criteria of the 2018 international consensus group is a clinician-rated evaluation based on 4 criteria. First, a quantitative reduction of goal-directed activity in comparison to the patient's previous level of functioning must be observed. Second, symptoms must persist for at least four weeks and affect at least two of the three apathy dimensions among a behavior/cognition, emotion or social dimension. Third, apathy should cause identifiable functional impairments. Finally, apathy should not be fully explained by other factors, such as effects of a substance or major changes in the patient's environment.

1.2 Connectivity analyses adding the MADRS score as covariate

As requested by a reviewer, we performed connectivity analyses adding the MADRS total score as covariates and found evidence for multicollinearity. All apathy scores were correlated with depression severity as expected (AMI: $r = 0.42$, AES: $r = 0.3$). Adding MADRS led to less robust estimation as the variance of the MADRS estimate was 40% to 70% higher than what could be expected without multicollinearity, and 20% to 60% higher for the apathy estimate (AES, AMI or DCA). To reduce the multicollinearity induced by adding the MADRS, we performed a principal component analysis on the MADRS scores. We found a dimension which gets the largest contribution from the lassitude and anhedonia items, together with concentration and vegetative symptoms, and is the third to explain the most of the total variance (13%). We selected this dimension and labeled it an "apathy dimension". As the first and third dimensions relates respectively to mood and apathy, we plotted the correlation of the

total items of the MADRS against the first and third principal components to identify the items which were correlated to these dimensions. We found that the lassitude, anhedonia, concentration and tension items had a similar direction of their projection in both dimensions. We thus chose the MADRS without these items as a covariate for depression severity in the subsequent connectivity models. We performed a multiple regression adding the MADRS modified score as covariate and found reduced multicollinearity in the models tested. We then ran TFNBS adding this modified MADRS score, with 1000 permutations instead of 5000 in our original analysis, and found that the brain hubs common to the three scales are comparable between the models with and without the covariates. The connectivity results are presented in **Table S5** and **Figure S6**. As the addition of the modified MADRS score did not provide a significant gain to the original results while being subject to a lack of robustness because of the exploratory selection of items and adding small variance to the estimator, we report these results in the **Supplementary Material** but not in the **Main Manuscript**.

2. Supplementary Results

2.1 Disconnected brain subnetworks between late-life depression and healthy controls

For the DMN intra-network connectivity, the NBS identified four subnetworks associated with the LLD group ($p_{\text{five-corrected}} < 0.001$, **Table S1, Fig. S3**), consisting of 416 regions. Post-hoc analyses suggest that intranetwork connectivity decreases in the LLD group, mainly for prefrontal polar areas (10_r, 10_d), frontal dorso-lateral areas (L_9M, L_9A), precuneus regions (31pd, 31pv) and in middle and superior temporal regions (TE1_m, TE1_a, TE2_a, TGd, STSva, STSvp). Conversely, parahippocampal and hippocampal regions were hyperconnected (PHA1, PHA2, EC, H).

For the CON intra-network connectivity, the NBS identified one subnetwork associated with the LLD group ($p_{\text{five-corrected}} < 0.0001$, **Table S1, Fig. S3**), comprising 72 regions. Post-hoc analyses suggest that, except for six regions, intranetwork connectivity decreases in the LLD group, notably for the middle insula (MI) and related fronto-opercular regions (FOP_4, FOP_5), the dorsolatero-prefrontal area B_46, the dorsofrontal regions 6_ma and 5_mv, and the mid-cingulum (33pr).

For the FPN intra-network connectivity, we identified one subnetwork associated with LLD ($p_{\text{five-corrected}} < 0.0001$, **Table S1, Fig. S3**), consisting of 48 regions. Post-hoc analyses suggest that intranetwork connectivity decreases in the LLD group for two main regions: the dorsolateral prefrontal areas p9-46v and IFJp. Conversely, the regions whose connectivity positively correlated with depression were the left anterior insula AVI, the lateral parietal region PFm, the region POS2, and the middle posterior temporal region TE1p.

2.2 Assessment of heterogeneity in detected subnetworks between apathy scales

Connectivity matrices for each resting-state network are presented in **Figure S5**. For the Default-Mode network (DMN), we found a pronounced tendency of hypoconnectivity associated with apathy severity across the three scales. Contrary to the AES, the AMI and DCA scores had a subset of regions which connectivity was positively associated with apathy. However, these positive associations were not robust across both scales. Concerning the fronto-parietal network (FPN), we observed a high similarity between the AES and the DCA, with increased connectivity associated with apathy. On the other hand, the AMI scale was more heterogeneous, with overall hypoconnected ROIs except between regions L_s6-8 and L_i6-8, and L_a10p and L_p10p. Both pairs of ROIs are involved in motor control and working memory of spatial information which might be impeded in apathy in LLD. These results suggest that FPN hyperconnectivity might mediate social apathy in LLD. The heterogeneity between the scales also suggests that the third-person observation of apathy provides more concordant results on FPN activity associated with apathy than self-rated AMI. For the Cingulo-opercular network (CON), we observed an increased connectivity for both the AES and the AMI scales, but with larger effect sizes for the AMI scale. This suggests that CON activity is impaired for social oriented-behavior in LLD apathy. As the CON is also implied in interoceptive processing, an alternative explanation would be that, being a self-rated scale, higher AMI scores might be associated with higher self-perception of apathy and thus hyperactivity at rest within the CON.

Table S3 reports the percentage of shared regions and shared direction of the effect size in intra-network connectivity between each pair of apathy scale (*i.e.* positive or negative association). We observe that the percentage of shared regions is less than 15% for each pair of scale. When comparing the intersection between the three scales, we have less than 5% of common ROIs between the scales. Concerning the proportion of shared association between apathy and brain regions connectivity, we observe that approximately half of the regions has similar associations with apathy for each scale-to-scale comparison in the DMN and FPN. However, when compared between the three scales of apathy, we observe that less than 20% of the ROIs have similar association with apathy. For the CON, we only found a subnetwork associated with the scores at AES and the AMI. For this scale, 13% of the detected ROIs had the same direction of the associations with apathy.

Supplementary Tables

Table S1: TNFBS identified subnetworks associated with apathy in the depression group

Brain Networks	Apathy Diagnostic criteria				AMI				AES				Depression			
	Num. Edges	pFWE	Strength pFWE	Num. Edges	pFWE	Strength pFWE	Num. Edges	pFWE	Strength pFWE	Num. Edges	pFWE	Strength pFWE	Num. Edges	pFWE	Strength pFWE	
DMN	154	0.99	***	154	0.99	***	154	0.99	***	416	0.96	***				
CON	72	0.98	0.08	72	0.99	***	72	0.99	0.003	72	0.98	***				
FPN	47	0.99	***	48	0.97	***	48	0.96	***	48	0.96	***				
Somatomotor	36	0.92	0.04	35	0.96	0.02	36	0.91	0.04	32	0.98	0.04				
Goal-oriented Behavior Network	36	0.9	***	35	0.97	0.001	32	0.99	0.0004							

AES: Apathy Evaluation Scale; **AMI:** Apathy Motivation Index; Num. Edges – number of edges in the subnetwork associated with a given variable; pFWE – FWE p-values for the number of edges in the subnetwork; Strength FWE - FWE p-values for the subnetwork strength (i.e. the sum of edges in the subnetwork). Significant p-values ($p < 0.003$) are reported in bold; for $p < 0.0001$: ***.

Table S3: Proportion of shared and different components identified by TFNBS between apathy scale

RSN	Comparison	Percentage of shared regions	Percentage of different regions	Percentage of shared direction of the effect	Percentage of different direction of the effect
DMN	AES-AMI	6.35	93.64	44.19	55.81
	AES-DCA	9.06	90.93	53.38	46.61
	AMI-DCA	7.84	92.15	49.22	50.78
	Total	1.85	98.15	15.62	84.38
FPN	AES-AMI	11.88	88.12	44.87	55.13
	AES-DCA	9.71	90.29	41.25	58.75
	AMI-DCA	13	87	63.77	36.23
	Total	4.63	95.37	16.49	83.5
CON	AES-AMI	14.28	85.71	13.27	86.7

For each resting-state network intranetwork connectivity, we report the proportion of shared regions detected by TFNBS and the proportion of shared direction of the association between each apathy scale combination taken two-by-two and all together. **AES**: Apathy Evaluation Scale; **AMI**: Apathy Motivation Index; **DCA**: Diagnostic criteria of apathy; **RSN**: Resting-state Network.

Table S4: Proportion of shared components identified by TFNBS with and without modified MADRS as covariate

RSN	Scale	Percentage of shared regions	Percentage of similar effect
DMN	AES	99.22	99.19
	AMI	99.03	98.93
	DCA	98.79	97.01
FPN	AES	99.58	99.15
	AMI	99.15	99.15
	DCA	98.52	97.56
CON	AES	99.44	99.37
	AMI	99.16	99.16

For each resting-state network intranetwork connectivity, we report the proportion of shared regions detected by TFNBS and the proportion of shared direction of the association between the results with the MADRS as covariate and without the MADRS as a covariate. **AES**: Apathy Evaluation Scale; **AMI**: Apathy Motivation Index; **DCA**: Diagnostic criteria of apathy; **RSN**: Resting-state Network.

Figures

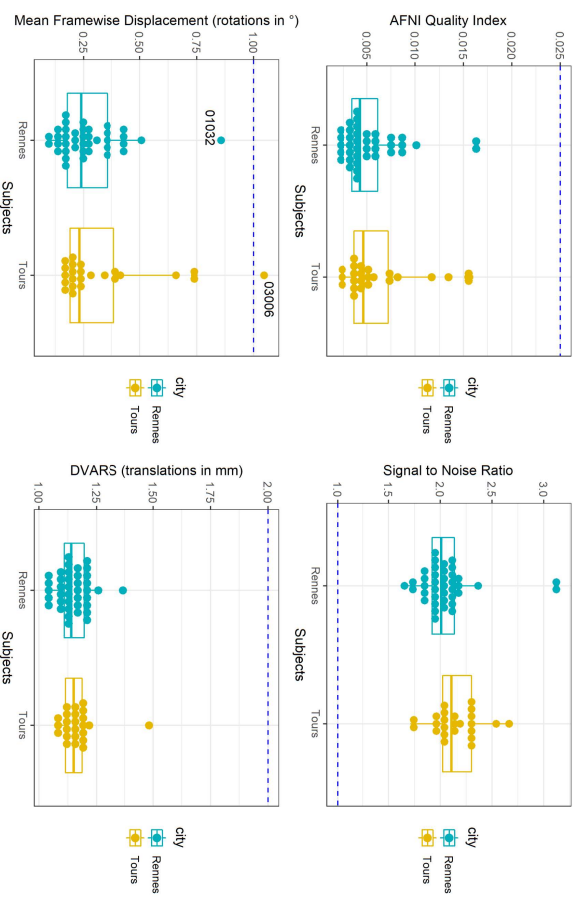


Fig S1. Quality control of fMRI data

Quality control results are summarized in Figure S1. Overall, participants had high quality fMRI data. Exclusion criteria were specified as an “aqi” index > 0.025 , a signal to noise ratio > 1 , a root-mean-square head motion less than 2mm for translations and less than 1° for rotation. The “aqi” index is AFNI’s mean quality index computed by the *3dTqual* routine. With these criteria, one LLD participant (03006) was removed for excessive head motion.

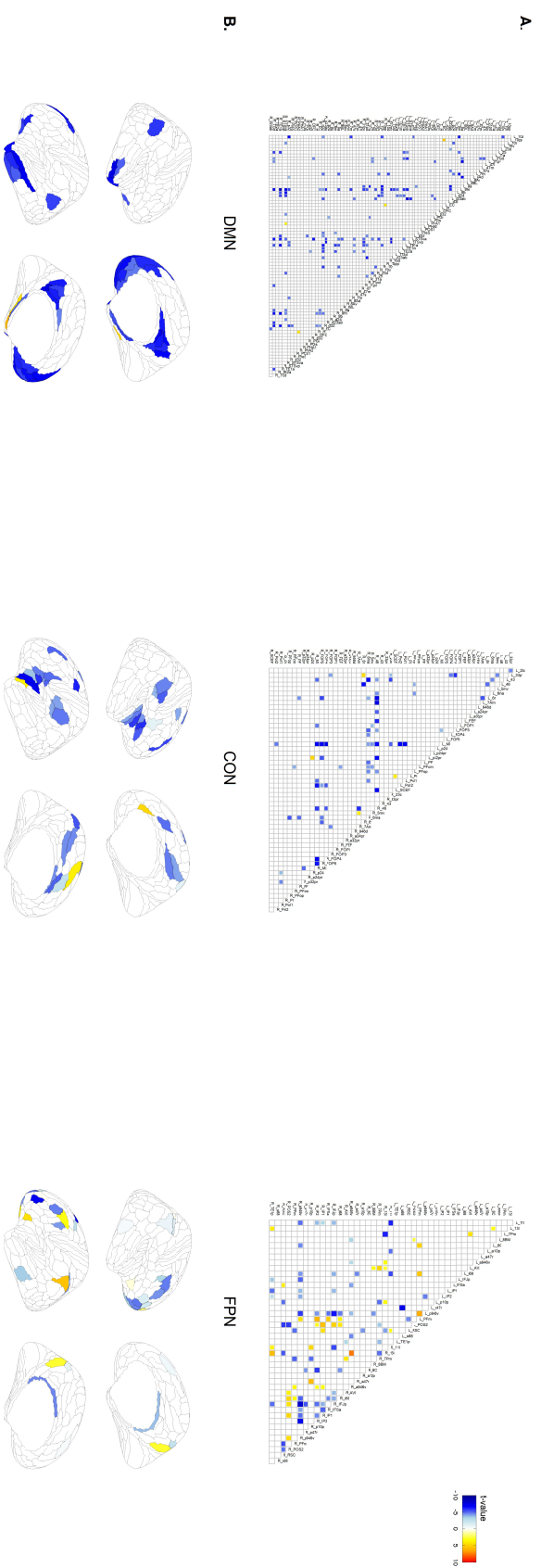


Fig S2. Subnetworks associated with late life depression

A. Brain regions whose connectivity is significantly modified in late-life depression for each resting-state network. For interpretation purposes, the effect size of the association between ROI-to-ROI connectivity and the depression group is represented in color. **B.** The same brain regions are represented on the Glasser atlas (except for L_10pp). For interpretation purposes, the marginal mean effect of each ROI associated with the depression group is represented in color). Brain regions belonging to the network are delimited in red. **Acronyms:** CON: cingulo-opercular network, DMN: default-mode network, FPN: fronto-parietal network.

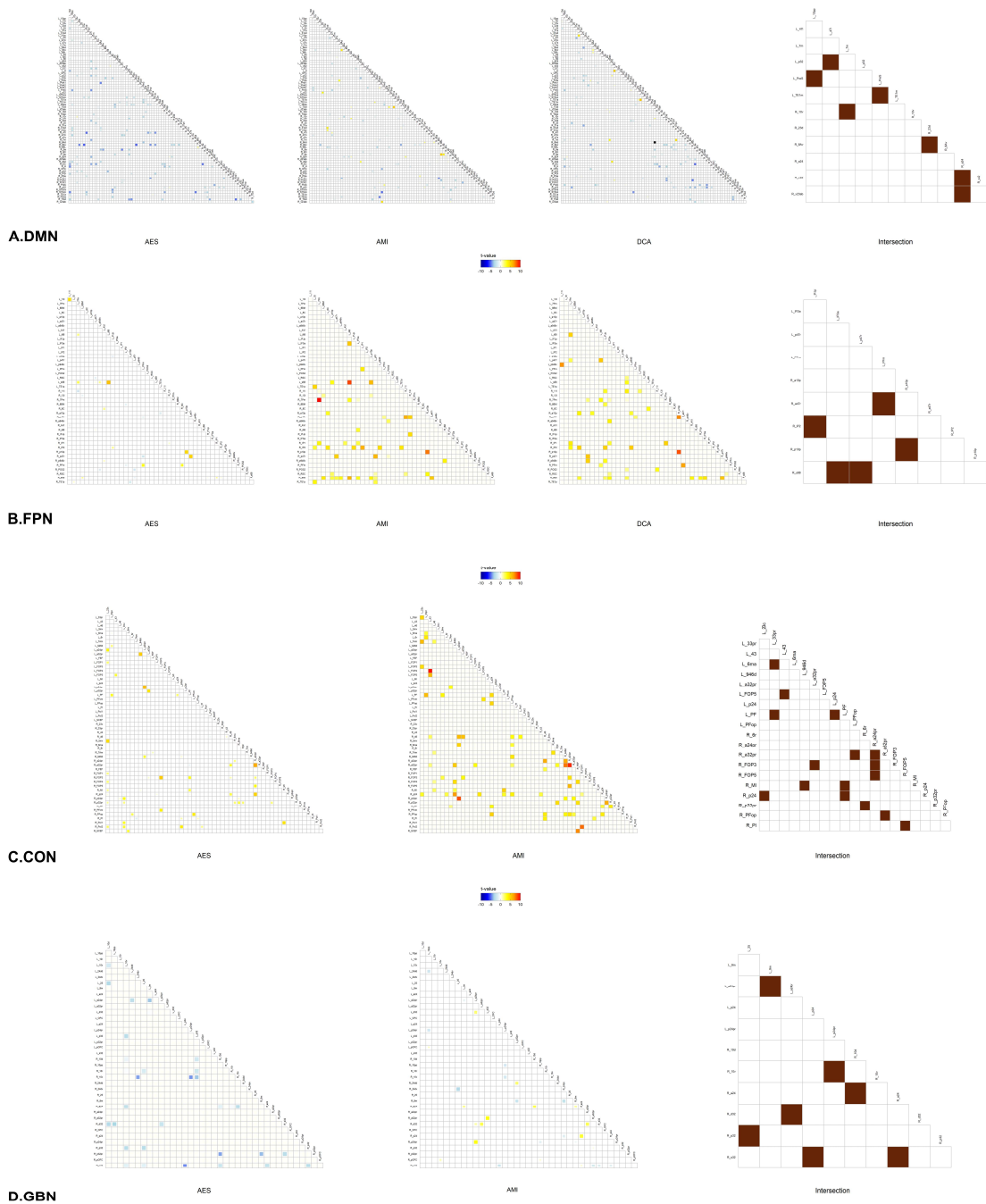


Fig S3. Subnetworks associated with apathy for each apathy scale

Brain regions whose connectivity is significantly associated with apathy for each resting-state network: **A.** for the DMN, **B.** for the FPN, **C.** for the CON and **D.** for the GOB goal network. Connectivity matrices are reported for each scale as well as the intersection between the scales. **Acronyms:** AES: Apathy Evaluation Scale, AMI: Apathy Motivation Index, CON: cingulo-opercular network, DCA: 2018 Diagnostic Criteria for Apathy, DMN: default-mode network, FPN: fronto-parietal network.

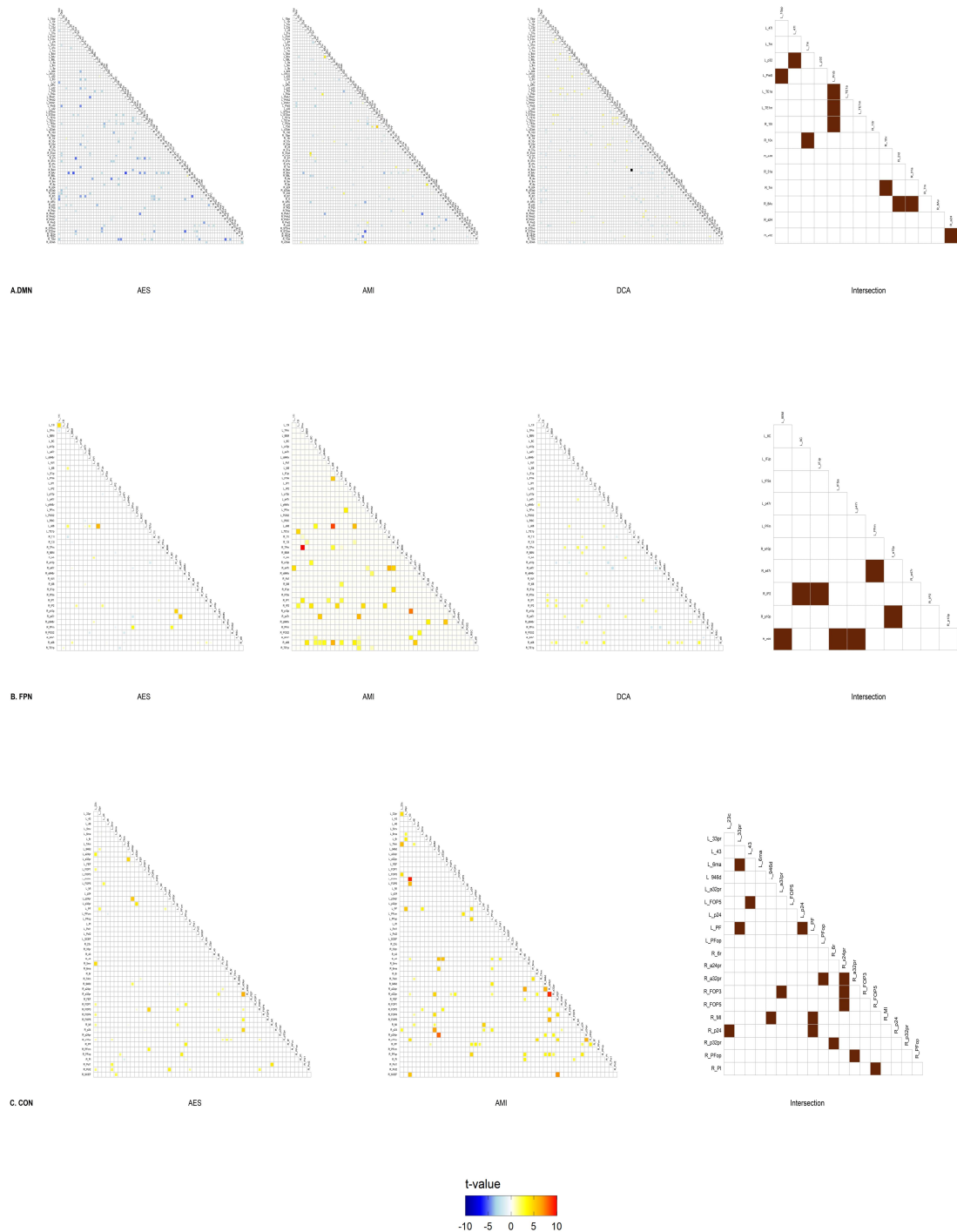


Fig S4. Subnetworks associated with apathy with MADRS as covariate

Brain regions whose connectivity is significantly modified in late-life depression for each resting-state network adding the modified MADRS as covariates; **A.** for the DMN, **B.** for the FPN and **C.** for the CON. Connectivity matrices are reported for each scale as well as the intersection between the scales. **Acronyms:** AES: Apathy Evaluation Scale, AMI: Apathy Motivation Index, CON: cingulo-opercular network, DCA: 2018 Diagnostic Criteria for Apathy, DMN: default-mode network, FPN: fronto-parietal network.

SUPPLEMENTARY MATERIAL STUDY 2

1. Supplementary Methods

1.1 MRI acquisition

1.2 Preprocessing MRI data

1.3 Statistical Methods

Supplementary Table

Table S1. Model fits comparison for predicted smoothed accelerometry data

Supplementary Figures

Figure S1. Examples of predicted smoothed accelerometry data from the selected model

1. Supplementary Methods

1.1 MRI acquisition

All participants underwent Magnetic Resonance Imaging on 3T scanners of the same brand and model at both sites (Magnetom Siemens Prisma, VE11C, Erlangen, Germany) and 64-ch head coils to reduce variability between the sites.

A whole brain T1-weighted MPRAGE image was acquired with repetition time (TR) = 1.9 sec, echo time (TE) = 2.26 msec, inversion time (TI) = 900ms, flip angle = 9°, 1 mm isotropic, field-of-view (FOV) = 256x256 mm², 176 slabs. During resting-state fMRI scanning, subjects were instructed to keep their eyes open, remain still as much as possible, not think of anything, and not fall asleep. Transverse echo-planar imaging (EPI) images with opposite polarities of the phase encoding direction were acquired with a multiband accelerated EPI sequence with the following parameters: TR= 1224 msec, TE= 30 msec, flip angle = 65°, multiband acceleration factor 3, in-plane resolution= 2.5 mm² isotropic, FOV = 210x210 mm², 54 axial slices with a thickness of 2.5 mm. A total of 288 volumes were collected in 6 minutes, plus 12 sec for the reversed phase.

During diffusion MRI, a CUbe and SPHERE (CUSP-66) sequence (Scherrer & Warfield, 2012) was acquired with 1.5mm isotropic resolution, an acquisition matrix size of 148x148x90, 60 gradient orientations, 7 b₀ with an anterior-posterior phase encoding direction and an extra b₀ with a reversed posterior-anterior phase for distortion correction purpose. The specificity of this sequence resides in its 60 gradients that are placed on a sphere and a cube *i.e.* with multiple gradient b-values ranging from 1000 to 3000s.mm⁻¹ contrary to classic diffusion MRI with a single shell (one sphere, one b-value) or with multiple shells such as human connectome project data with 3 spheres, 3 b-values (Sotiropoulos, 2013).

1.2 Preprocessing of MRI data

Preprocessing of anatomical images consisted in skull-stripping using an atlas-registration-based method by transforming the structural image of each patient to the atlas image, using the linear and non-linear block-matching algorithm (Commowick et al., 2012; Ourselin et al., 2000) available in the open source software for medical image processing called Anima (<https://github.com/Inria-Visages/Anima-Public/wiki>).

For the fMRI images, the following preprocessing steps were performed. The first four volumes from each subject were discarded by the scan machine to allow the signal to reach equilibrium and the participants to adapt to the scanning noise. A fieldmap was estimated based on two EPI references with opposing phase-encoding directions using *topup* (Andersson et al., 2003). The estimated fieldmap was

applied to the fMRI images using *fugue* (Jenkinson et al., 2002). Head-motion parameters with respect to the median or mean fMRI volume (transformation matrices, and six corresponding rotation and translation parameters) were estimated before applying spatiotemporal filtering using *mcflirt*. BOLD runs were slice-time corrected using *slicetimer*. A bandpass filtering was applied to the BOLD signal to filter time series frequencies between 0.01 and 0.1 Hz. The median fMRI volume was co-registered to the participant's structural image, using a rigid body transformation model (6 parameters). The structural image was then transformed to the Montreal Neurological Institute (MNI) template, using the linear and non-linear block-matching algorithms (Commowick et al., 2012; Ourselin et al., 2000). For each subject, two image transformations were computed: the transformation from the mean functional volume to the structural volume and the transformation from the individual structural volume to the MNI template. By concatenating the above transformations sequentially, we obtained a direct transformation from each initial functional volume to the MNI space. The inverse of the transformation was applied to the Glasser atlas (Glasser et al., 2016) to register this atlas in the fMRI native space. After these steps, nuisance regression was performed with 3 kinds of regressors. Residual motion was removed with the parameters estimated by FSL's *mcflirt*, computed by backwards differences (6 regressors). The physiological noise was reduced using regressors calculated by the CompCor method (Behzadi et al., 2007), implemented in nilearn (<http://nilearn.github.io/>). These 5 regressors correspond to the principal components from noisy regions-of-non-interest, such as white matter, cerebral spinal fluid and non-brain signals. The global signal was included as a regressor by inspection of the connectivity matrix. Individual structural and functional images were inspected to remove subjects with significant artifacts or lesions. Participants were excluded if any of the following image quality metrics were above/below the specified threshold. Exclusion criteria were specified as an AFNI's mean quality index("aqi") index > 0.025, computed by the *3dTqual* routine (Cox, 1996), a signal to noise ratio < 1, a root-mean-square head motion above 2mm for translations and 1° for rotation, as accepted in elderly population (Doucet et al., 2021). With these criteria, 3 LLD subjects were excluded, two for significant artifacts and one for excessive head motion.

For diffusion images, the preprocessing pipeline consisted of these following steps, using the Anima software. Eddy current correction was performed by registering linearly then non-linearly each sub-volume of the CUSP data to the first sub-volume (Andersson & Sotiropoulos, 2015). Each non-linear transformation is computed only in the phase encoding direction. Then, distortion correction was designed to register two b_0 images of opposite phase encoding directions using a block-matching correction (Hedouin et al., 2017). The transformation was applied to all diffusion-weighted images volumes to obtain an unwrapped volume. Denoising was based on a 3D optimized blockwise version of the non-local means filter using the redundancy of information to remove the noise (Wiest-Daesslé et al., 2008). Finally, a rigid transformation was computed between the structural image and the

diffusion-weighted image volume of the subject, and the composition of the two transformations was finally inversely applied to the atlas mask to obtain the diffusion-weighted mask.

1.3 Statistical Methods

Threshold-free Network Based Statistics

The functional connectivity measures between any pair of ROIs were estimated using a Pearson's correlation. A Fisher's r-to-z transformation was applied to normalize the coefficients. The threshold-free network-based statistics (TFNBS) (23,24) combines the network-based statistics approach (23) and the threshold-free cluster enhancement algorithm adapted for graphs. The algorithm computes the likelihood of each set of connected edges that surpass an initial statistical threshold, also referred to as components of interest (COI). Such likelihood estimation is based on the number of connected edges and how it compares to a null distribution generated by permutations of the original data. However, contrary to NBS, an adaptive threshold was implemented without having to set arbitrary a priori thresholds. The method consists of the 4 following steps (see Baggio et al., 2018): (i) The z-scores are corrected for confounders of age, gender and education using a linear regression method. The association between the principal component score and the COI is investigated by three distinct linear models, one per resting state network. (ii) A threshold is applied to the obtained F-statistics matrix at a series of steps h , with a step interval defined as a hundredth of the maximum value of the matrix. (iii) At each thresholding step, the value of each matrix suprathreshold element belonging to a connected component is replaced by the component's number of connections raised to the power E , multiplied by the component's height raised to the power H . As recommended (Baggio et al., 2018), the E parameter values were set to 0.75 combined with H parameter values of 3.25. (iv) The matrices obtained at each step were subsequently summed giving the final TFNBS score for every network edge. Statistical significance was established through permutation testing over 10000 permutations. At each permutation, principal component score was shuffled across subjects, and the steps above repeated. FWE-corrected p-values were obtained by comparing each connection's TFNBS score with the null distribution of maximal sub-connectome-wise scores at each permutation. The alpha FWE-corrected p-value for statistics significance of the network was set as $0.05 / \text{number of models}$.

2. Supplementary Tables

Model	Degrees of freedom	AIC	MSE	Mean out-of-sample deviance
Mod_S	487	511 440	0.45	13 178
Mod_I	392	562 348	0.45	13 260
Mod_GI	355	562 745	0.45	13 470
Mod_G	48	568 422	0.47	15 573
Mod_GS	1143	527 011	2.26	16 421

Table S1. Model fits comparison of predicted smoothed accelerometry data

We compared five generalized additive models of motor activity as a function of time: model G (*mod_G*) corresponding to a global smoother across subjects, model GS (*mod_GS*) which has a global smoother plus group-level smoothers that have the same wiggleness (or a shared penalty), model GI (*mod_GI*) which has a global smoother plus group-level smoothers with individual wiggleness (or individual penalties), model S (*mod_S*) with group-specific smoothers without a global smoother but with the same wiggleness, and model I (*mod_I*) corresponding to group-specific smoothers with different wiggleness. Model I was selected for principal component analysis as it had the lowest AIC, MSE and mean out-of-sample deviance. **Acronyms:** AIC: Akaike Information Criterion; MSE: Mean-Squared Error.

2. Supplementary Figures

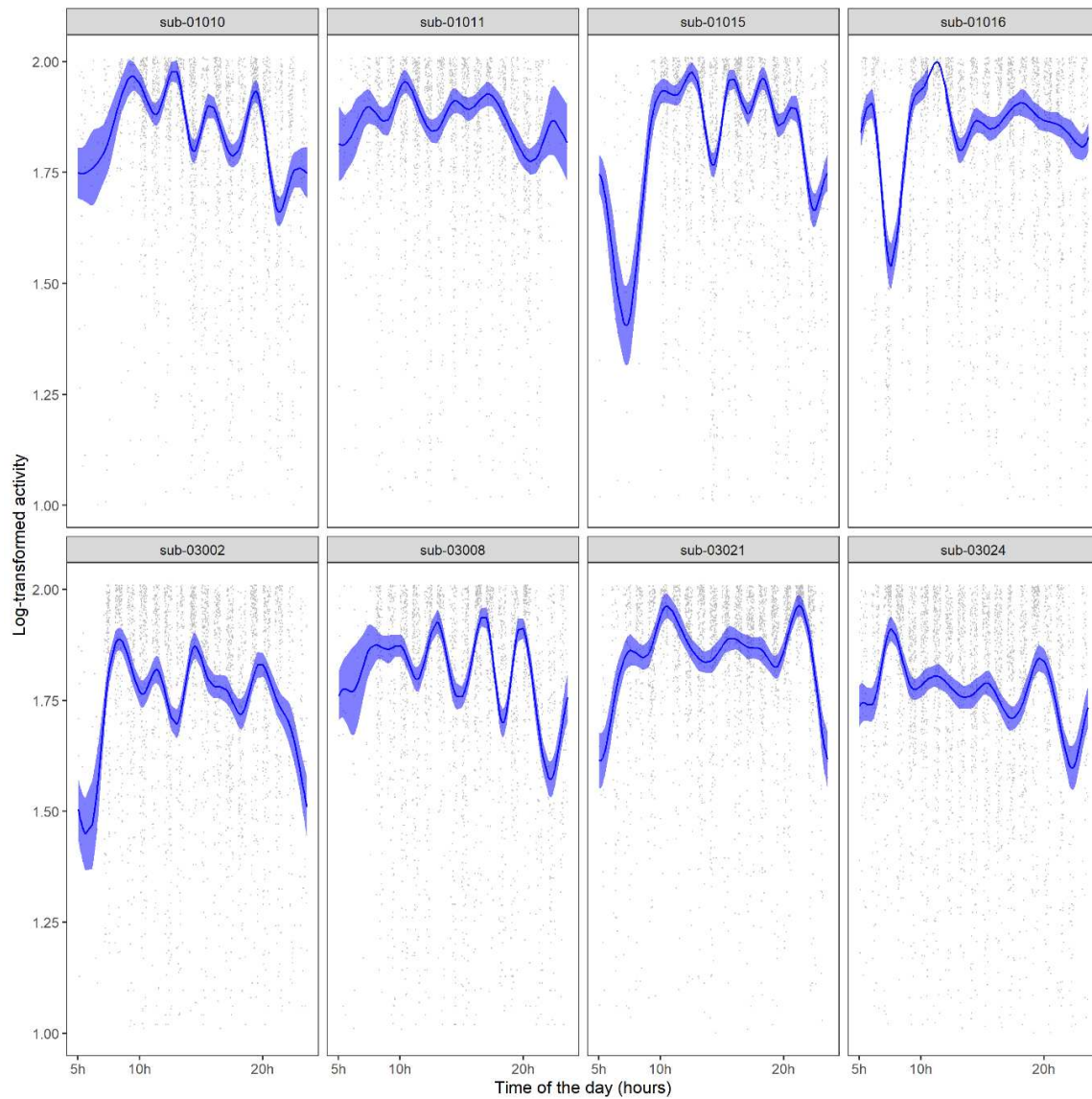


Figure S1. Examples of predicted smoothed accelerometry data from the selected model

Mean \pm 2 standard errors of the predicted smooth activity as a function of time from model S are reported, against observed activity in eight randomly selected patient (4 from Rennes and 4 from Tours).

2. Supplementary Figures

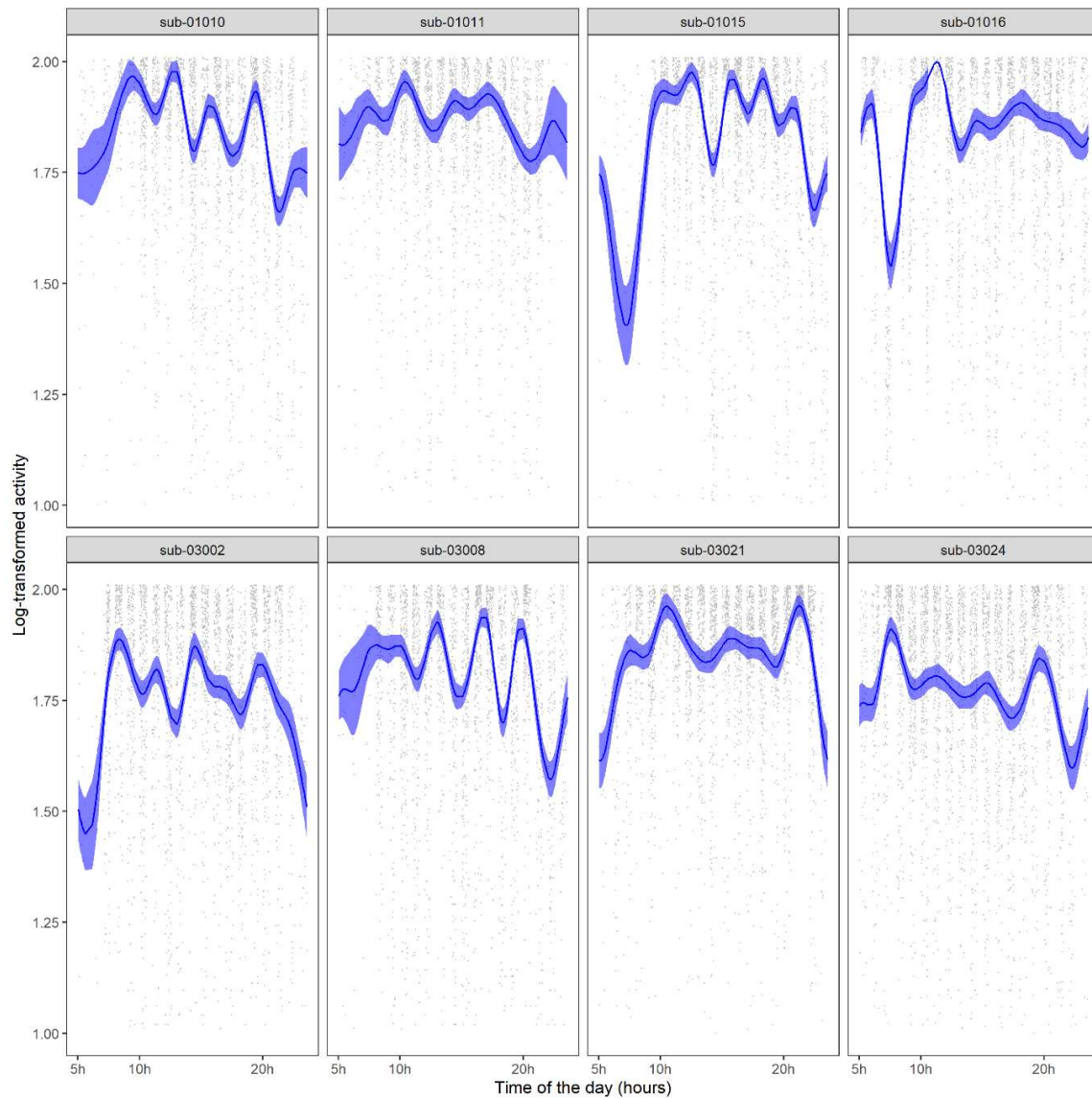


Figure S1. Examples of predicted smoothed accelerometry data from the selected model

Mean \pm 2 standard errors of the predicted smooth activity as a function of time from model S are reported, against observed activity in eight randomly selected patient (4 from Rennes and 4 from Tours).

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Titre : Apathie et dépression du sujet âgé : nouveaux biomarqueurs en actimétrie et en imagerie cérébrale (ACTIDEP)

Mots clés : Dépression, sujet âgé, imagerie par résonance magnétique, actimétrie

Résumé : Une meilleure compréhension de l'apathie dans la dépression du sujet âgé aiderait à prédire l'évolution péjorative de ce trouble, telle que la démence ou la dépression persistante. L'actimétrie permet une évaluation objective et écologique de l'activité motrice, mais doit encore être évaluée dans la dépression du sujet âgé. Les objectifs de cette thèse étaient de relier différentes mesures d'apathie à la connectivité cérébrale fonctionnelle, d'évaluer la relation entre l'activité motrice et les mesures d'apathie, et de relier l'activité motrice à la connectivité cérébrale fonctionnelle de repos et structurelle. Pour ce faire, une étude transversale a été réalisée où des sujets âgés souffrant de dépression ont pu bénéficier d'une évaluation psychiatrique d'apathie, d'une IRM cérébrale

fonctionnelle, ainsi que d'un enregistrement de leur activité motrice. Les résultats de cette étude indiquent que l'apathie est associée à des changements de connectivité cérébrale fonctionnelle dans des régions du cerveau impliquées dans les comportements dirigés vers des objectifs. L'activité motrice moyenne ainsi que le chronotype étaient associés à l'apathie ainsi qu'à des modifications fonctionnelles des mêmes réseaux cérébraux. Ces résultats suggèrent que différentes dimensions de l'apathie peuvent être associées à des altérations spécifiques de la connectivité et que l'actimétrie est un outil permettant d'explorer ces dimensions et générer de nouvelles hypothèses sur ce trouble.

Title : Apathy in late-life depression: new biomarkers using actimetry and magnetic resonance imaging

Keywords : Depression, old-age, magnetic resonance imaging, actimetry

Abstract : A better understanding of apathy in elderly depression would help predict the pejorative course of this disorder, such as dementia or persistent depression. Actimetry provides an objective and ecological assessment of motor activity, but still needs to be evaluated in elderly depression. The objectives of this thesis were to link different measures of apathy to functional brain connectivity, assess the relationship between motor activity and apathy measures, and relate motor activity to resting-state functional and structural brain connectivity. To achieve this, a cross-sectional study was conducted in which elderly subjects with depression underwent a psychiatric evaluation of apathy, functional brain MRI,

and recording of their motor activity. The results of this study indicate that apathy is associated with changes in resting-state brain connectivity in regions of the brain involved in goal-directed behaviors. Average motor activity and chronotype were associated with apathy as well as functional alterations in the same brain networks. These results suggest that different dimensions of apathy may be associated with specific connectivity alterations, and that actimetry is a useful tool to explore these dimensions and generate new hypotheses about this disorder.