



HAL
open science

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

Jean-Charles Roy, Renaud Hédouin, Thomas Desmidt, Sébastien Dam, Iris Miréa-Grivel, Weyl Louise, Elise Bannier, Laurent Barantin, Dominique Drapier, Jean-Marie Batail, et al.

► To cite this version:

Jean-Charles Roy, Renaud Hédouin, Thomas Desmidt, Sébastien Dam, Iris Miréa-Grivel, et al.. Quantifying Apathy in Late-Life Depression: Unraveling Neurobehavioral Links through Daily Activity Patterns and Brain Connectivity Analysis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 2024, pp.1-30. 10.1016/j.bpsc.2024.04.002 . hal-04564336

HAL Id: hal-04564336

<https://hal.science/hal-04564336v1>

Submitted on 24 Sep 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

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

Jean-Charles Roy, Renaud Hédouin, Thomas Desmidt, Sébastien Dam, Iris Mirea-Grivel, Louise Weyl, Elise Bannier, Laurent Barantin, Dominique Drapier, Jean-Marie Batail, Renaud David, Julie Coloigner, and Gabriel H. Robert

ABSTRACT

BACKGROUND: Better understanding apathy in late-life depression would help improve prediction of poor prognosis of diseases such as dementia. Actimetry provides an objective and ecological measure of apathy from patients' daily motor activity. We aimed to determine whether patterns of motor activity were associated with apathy and brain connectivity in networks that underlie goal-directed behaviors.

METHODS: Resting-state functional magnetic resonance imaging and diffusion magnetic resonance imaging were collected from 38 nondemented participants with late-life depression. Apathy was evaluated using the diagnostic criteria for apathy, Apathy Evaluation Scale, and Apathy Motivation Index. Functional principal components (fPCs) of motor activity were derived from actimetry recordings taken for 72 hours. Associations between fPCs and apathy were estimated by linear regression. Subnetworks whose connectivity was significantly associated with fPCs were identified via 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 2 fPCs associated with apathy: mean diurnal activity, negatively associated with Apathy Evaluation Scale scores, and an early chronotype, negatively associated with Apathy Motivation Index scores. Mean diurnal activity was associated with increased connectivity in the default mode, cingulo-opercular, and frontoparietal networks, while chronotype was associated with a more heterogeneous connectivity pattern in the same networks. We did not find significant associations between microstructural metrics and fPCs.

CONCLUSIONS: Our findings suggest that mean diurnal activity and chronotype could provide indirect ambulatory measures of apathy in late-life depression, associated with modified functional connectivity of brain networks that underlie goal-directed behaviors.

<https://doi.org/10.1016/j.bpsc.2024.04.002>

Late-life depression (LLD) represents a public health concern given its high prevalence and detrimental impact on well-being (1,2). Apathy, defined by diminished motivation and 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 that underlie apathy in LLD is essential for accurately stratifying individuals with LLD and preventing negative outcomes associated with apathy. To accurately measure apathy, it is necessary to go beyond self-reported and heteroquestionnaires. Questionnaires may lack accuracy in measuring goal-directed behaviors related to brain mechanisms, which can affect their construct validity (8,9), and are 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 for estimating patterns of motor activity associated with apathy in dementia and psychiatric disease. For example, earlier waking and bedtime schedules, as well as bimodal diurnal activity, have been associated with apathy in Alzheimer's disease (11) and in mild cognitive impairment (12) and were predictive of decreased cognition in a community sample of older adults (13). However, motor activity and apathy are complex phenomena that require comprehensive measurement of apathy. Because apathy is a debated concept (11,12) and the scales that measure it have distinct psychometric properties, we decided to incorporate 3 complementary measures of apathy: the Apathy Evaluation Scale (AES) (13), which defines apathy as a subjective reduction of motivation; the Apathy Motivation Index (AMI) (14), which captures engagement in social interactions; and the diagnostic criteria

for apathy (DCA) (9), which provide a clinical account of the functional impairment induced. As shown in a previous study (15), the choice of which apathy scale to use may have direct implications for the underlying biological mechanisms that are relevant, such as functional brain connectivity, and could be helpful for dissociating common components of apathy from the specific characteristics of each scale.

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 ecologically measured apathy. Apathy has been associated with increased resting-state functional connectivity (rsFC) between the anterior cingulate cortex (ACC) and anterior insular and orbital cortices but decreased rsFC with prefrontal lateral regions (15–17). Higher rsFC between the anterior insula and the right dorsolateral prefrontal cortex (DLPFC) and premotor regions but reduced rsFC with the bilateral parietal posterior regions was also correlated with apathy (18,19). In LLD, hypoconnectivity between the dorsal ACC (dACC) and DLPFC is correlated with poorer executive functions (20) and apathy during effortful emotion recognition (17). Moreover, diffusion MRI can identify and elucidate the white matter microstructure modifications associated with apathy in LLD (21), such as reduced anisotropy of the splenium of the corpus callosum and cingulum (15). These results suggest that apathy in LLD is underpinned by modifications in functional and structural connectivity of goal-oriented networks, namely the default mode network (DMN), frontoparietal network (FPN), and cingulo-opercular network (CON). However, it remains unclear whether objective patterns of motor activity in LLD could capture impaired connectivity in these networks.

We proposed to integrate brain connectivity and accelerometry to unravel the neural mechanisms that underlie apathy in LLD. To this end, we recorded the motor activity of participants with LLD for 3 days. We estimated the association between PCA scores of 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, similar to those outlined in apathy in dementia, would be correlated with the functional and structural networks underlying goal-oriented behaviors. This study is a continuation of a previous study (15) investigating the association between apathy and rsFC in LLD.

METHODS AND MATERIALS

Participants

Thirty-eight patients with LLD were recruited from the French old-age psychiatry centers of Rennes (25 participants) and Tours (13 participants) between October 2019 and April 2022. Inclusion and exclusion criteria were assessed during a psychiatric interview conducted by a trained geriatric psychiatrist. Inclusion criteria were age >60 years with DSM-5 and Mini-International Neuropsychiatric Interview criteria for major depressive disorder. Noninclusion criteria comprised DSM-5 criteria for major cognitive disorder and Mattis Dementia

Rating Scale <125; neurological diseases; inflammatory or mechanical diseases impeding motor activity; severe sarcopenia defined as a walk test <1 m/second; extrapyramidal symptoms assessed by the Unified Parkinson's Disease Rating Scale – Part III; having an antipsychotic prescription; high suicidality defined as a Clinical Global Impression Suicide Scale score >4; legal protection, deprived of liberty; and MRI contraindications. Written informed consents were collected. The study was approved by the relevant institutional review board (ID-RCB 2018-AO2643-52, [NCT03807167](#)).

Procedure

After inclusion, each participant underwent a neuropsychological assessment, and their motor activity was recorded for 72 hours using an accelerometer (wGT3X-BT; ActiGraph) worn on the nondominant wrist. On the last day of recording, patients underwent a structural and rs-fMRI scan.

Clinical Assessment. During the psychiatric interview, apathy was assessed by the DCA of the 2018 international consensus group (9), the clinician-rated version of the AES (13), and the AMI (14). These measures provide complementary evaluations of apathy, with the AES evaluating the cognitive, behavioral, and emotional dimensions of apathy, the AMI adding a social dimension of apathy, and the DCA considering functional impairment caused by apathy. Depression severity was measured via the Montgomery–Åsberg Depression Scale (22).

Participants' cognitive profiles were established by trained neuropsychologists. Executive functions were evaluated by the Modified Wisconsin Card Sorting Test (23) for planning and set shifting, the Trail Making Test (24) A and B for speed processing and cognitive flexibility, and the Stroop test for cognitive control (25). Language was evaluated via semantic and phonemic verbal fluencies (26).

MRI Acquisition. All participants underwent MRI on 3T scanners of the same brand and model at both sites to reduce between-site variability. Whole-brain T1-weighted images were acquired by magnetization-prepared rapid acquisition gradient-echo with repetition time = 1.9 seconds, echo time = 2.26 ms, inversion time = 900 ms, flip angle = 9°, 1 mm isotropic, field of view = 256 × 256 mm², 176 slabs. Transverse rs-fMRI echo-planar images aligned with the anterior and posterior commissures were acquired with the following parameters: repetition time = 1224 ms, echo time = 30 ms, flip angle = 65°, multiband acceleration factor 3, in-plane resolution = 2.5 × 2.5 mm² isotropic, field of view = 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 was acquired by a 60-gradient multishell cube and sphere sequence (27) with 2-mm isotropic resolution, repetition time = 5216 ms, echo time = 54.4 ms, multiband acceleration factor 2, parallel imaging with generalized autocalibrating partially parallel acquisitions 2, field of view = 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

Activity and Brain Connectivity in Late-Life Depression

0 to 3000 s/mm², and 7 b0 with an anterior-posterior phase-encoding direction and an additional b0 with reversed (P > A) phase encoding.

Image Processing

Preprocessing of Accelerometry Data. Preprocessing of accelerometry data is detailed in [Supplemental Methods](#). To summarize, accelerometer data were measured every 30-second interval between 5 AM and midnight for 72 hours. One participant 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 (fPCs) 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 these variations quantitatively (28). The top 4 fPCs were selected (28). Individual scores for each component were calculated that summarized the participant's mean variation at each fPC.

Preprocessing of MRI Data. Details of the preprocessing of T1-weighted images, fMRI, and diffusion data, including motion correction and nuisance regression, are reported in [Supplemental Methods](#).

Brain Regions of Interest. For fMRI data, cortical regions of interest (ROIs) were selected from the asymmetric Human Connectome Project atlas (29) consisting of 360 ROIs. Following the Cole-Anticevic brain-network parcellation (30), we investigated the intranetwork connectivity of the DMN, CON, and FPN.

For diffusion MRI data, white matter segmentation was performed based on a convolutional neural network that segments tracts infields of fiber orientation distribution function peaks pretrained on high-quality diffusion images acquired for the Human Connectome Project and implemented in TractSeg (31). This algorithm was applied on preprocessed diffusion data after a rigid alignment on the Montreal Neurological Institute template. Based on previous studies of LLD or apathy (32–34), we selected 22 bundles of interest a priori: 7 parts from the corpus callosum comprising the rostrum, genu, posterior midbody, isthmus, and splenium; the anterior commissure; bilateral cingulum; bilateral superior longitudinal fascicles (divided into 3 parts); bilateral inferior longitudinal fascicles; bilateral corticospinal tracts; and bilateral uncinate fascicles.

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 scalar maps were derived from the DTI model (35). In NODDI, the diffusion signal is decomposed into 2 compartments: an anisotropic compartment corresponding to the intraneurite space and an anisotropic Gaussian space related to the extraneurite compartment including cell bodies (36). The NODDI-derived metrics are intracellular volume fraction

corresponding to neurite density and the orientation dispersion index representing angular variation of neurites.

Statistical Analyses

Participants' Characteristics. Demographic, clinical, and psychological data of participants with apathetic and non-apathetic LLD were compared using χ^2 tests for qualitative variables and independent t tests otherwise (or Mann-Whitney U tests if distributions were non-Gaussian).

Association Between Daily Activity and Apathy Scores. Three multiple linear regression models were tested with the apathy score as the dependent variable (AES, DCA, or AMI) and the fPC scores of accelerometry as independent variables (4 components), with age, sex, and years of education as covariates. The p value was set as .05/3 (number of networks tested). Results controlling for depression severity are reported in the [Supplemental Results](#).

Association Between Daily Activity and rsFC. Functional connectivity between ROIs was assessed using Pearson's correlations, normalized through r -to- z transformation. The association between fPC of motor activity and rsFC was estimated via threshold-free network-based statistics (TFNBS) (37,38) (detailed in [Supplemental Methods](#)). This method combines the network-based statistics approach (37) and the threshold-free cluster enhancement algorithm. It computes the likelihood that a set of connected edges associated with a variable surpasses a range of statistical thresholds, without having to choose an arbitrary threshold. The association between connectivity and fPC scores was corrected for age, gender, and education using linear regression. Statistical significance was established through permutation testing over 10,000 permutations. Familywise error (FWE)-corrected p values were obtained by comparing each connection's TFNBS score with the null distribution of maximal subconnectome-wise scores. The p value for the statistical significance of the network was set as .05/3.

While TFNBS provides a score to identify the significant subnetwork associated with a variable, it does not give the direction of the association. For interpretation, we reported the marginal mean effect at each ROI level. Marginal mean effects are conditional averages that correspond to the expected change in correlation for an ROI with all other ROIs for an increase of fPC scores, holding other predictor variables constant (39). To do this, a linear mixed-model effect was applied to the subnetwork detected by TFNBS 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 interest, adjusted for age, sex, years of education, and with the participant as a random intercept.

Information on statistical adjustment for depression duration is available in the [Supplemental Results](#).

Association Between Daily Activity and Diffusion MRI. For each bundle, the center line of the tract was computed using the minimum distance-flipped metric (40) and resampled to 100 equidistant segments. Microstructure metrics were projected on the center line via a cKDTree algorithm

(40). The association between the fPC scores of motor activity and diffusion metrics along the bundle was evaluated using a linear model with age, sex, and center as covariates. At each tract point, we used a nonparametric permutation-based statistical comparison with 5000 iterations to account for multiple comparisons given the correlative structure between adjacent points and the number of tracts tested (41). We report the number of clusters whose size exceeded the specified threshold with adjustment for the number of tracts and points.

RESULTS

Demographic Variables and Clinical Measures

Demographic and clinical characteristics of the LLD group are reported in Table 1. The mean age of the sample was 74 years, with 26 female and 12 male participants. The participants had

Table 1. Demographic and Clinical Characteristics of the LLD Group

	LLD, <i>n</i> = 38
Age, Years	74 [72–80.75]
Gender, Female:Male	26:12
Education, Years	12 [8–13.75]
Medical Comorbidities	
Cardiovascular	13%
Neurologic	0%
Pneumological	16%
Rheumatological	5%
Depression Characteristics	
Type of depression, MDD:bipolar disorder	31:7
Duration of depression, years	24 [4–40]
MADRS	25 [22–30]
Apathy	
AES	42 [37–50]
DCA	27:11
AMI	30 [18–36]
Psychotropic Drugs, 1 or More Per Participant	
Antidepressants	84%
Mood stabilizers	13%
Benzodiazepines	39%
Antipsychotic	11%
Cognitive Evaluation	
DRS	134 [128–137]
TMT-A	47.5 [36.0–64.8]
Stroop interference score	–73.5 [–97.3 to –54.8]
TMT B–A	80.0 [57.0–124.0]
MCST, perseverative errors	3.0 [1.0–5.8]
MCST, complete categories	6.0 [4.0–6.0]
Verbal Fluencies	
Semantic	23.5 [18.0–28.3]
Phonemic	18.0 [13.0–24.0]

Values are presented as *n*, %, or mean [minimum–maximum].

AES, Apathy Evaluation Scale; AMI, Apathy Motivation Index; DCA, diagnostic criteria for apathy; LLD, participants with late-life depression; MADRS, Montgomery–Åsberg Depression Rating Scale; MCST, Modified Card Sorting Test; TMT-A, Trail A of the Trail Making Test; TMT B–A, difference in scores between versions B and A of the TMT.

moderate to severe depression. Twenty-seven participants with LLD met the DCA criteria for apathy compared with 11 participants with nonapathetic LLD.

Association Between Patterns of Activity and Apathy in LLD

The first 4 components of motor activity, which explained 85% of the total variance, are presented Figure 1.

The first fPC (fPC1), which accounted for 51% of the variance in motor activity, identified participants' mean daily activity. The second fPC (fPC2), which explained 16% of the variance, distinguished participants with high morning activity and reduced evening activity (red curve) from participants with reduced morning activity and high evening activity (green curve). The third fPC, which explained 13% of the variance in motor activity, distinguished individuals with low activity at waking and before sleeping, associated with bimodal activity (red curve), from individuals with higher baseline and constant diurnal activity. The fourth fPC, which captured 6% of the variance, identified a pattern with high activity in the early afternoon and low activity in the late afternoon in participants with low activity in the early afternoon and high activity in the late afternoon.

Regarding the associations with apathy (Table 2) (significant results $p < .017$), we found a significant association between fPC1 and AES scores ($z_{37} = -3.37, p = .002$) and a tendency with DCA ($z_{37} = -2.50, p = .018$) suggesting that apathy severity was associated with reduced mean activity but not with AMI scores ($p = .07$). The fPC2 scores were negatively associated with AMI scores ($z_{37} = -2.78, p = .016$) but not with the other measures (all $ps > .017$), suggesting that apathetic individuals exhibited decreased motor activity during the morning and higher activity in the evening. We found no significant association between apathy and third or fourth fPC.

Association Between Motor Activity and rs-fMRI Intranetwork Connectivity in LLD

Association Between the First PC of Activity and Brain Intranetwork Functional Connectivity. The statistically significant results are reported in Figure 2A and Table S3.

For the DMN, we used TFNBS to identify 1 subnetwork associated with fPC1 scores (all $p_{FWE-corrected} < .0001$). Connectivity between regions of this subnetwork containing medial, lateroinferior, and superior prefrontal regions; inferior temporal regions; the posterior cingulate and cuneus; and inferoparietal cortices was negatively associated with reduced fPC1. The direction of the association between connectivity and motor activity varied between the left and right hemispheres for the hippocampus, parahippocampal regions, and the subgenual ACC.

For the CON, we used TFNBS to identify 1 subnetwork associated with fPC1 scores (all $p_{FWE-corrected} < .0001$). Connectivity between regions of this subnetwork was negatively associated with reduced fPC1 for insular regions, dorsal and mid ACC regions, and the left inferoparietal cortex. Connectivity was increased bilaterally in fronto-opercular regions and the dACC.

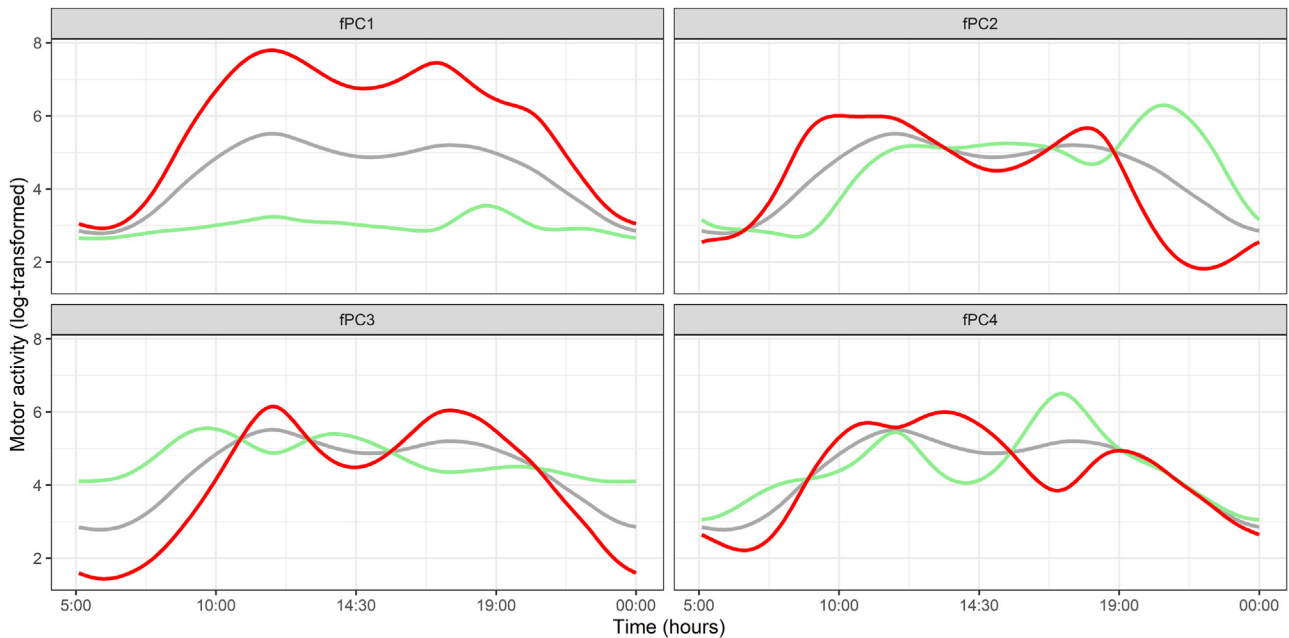


Figure 1. Functional principal components (fPCs) of motor activity in late-life depression. The first 4 components of the fPC analysis of actimetry. The PC functions are shown as perturbations of the mean activity (gray). The red curve shows what happens when a small amount of PC is added to the mean. Similarly, the green curve shows what happens when a small amount of PC is subtracted.

For the FPN, we used TFNBS to identify 1 subnetwork associated with fPC1 scores (all $p_{FWE-corrected} < .0001$). Connectivity between regions of this subnetwork was negatively associated with reduced fPC1 for bilateral parietal regions and the medial prefrontal region, right polar cortex, DLPFC regions, and left precuneus. Connectivity was increased in left prefrontal regions and in the right precuneus.

Association Between the Second PC of Activity and Brain Intranetwork Functional Connectivity Activity. The statistically significant results are reported [Figure 2B](#) and [Table S3](#).

For the DMN, we used TFNBS to identify 1 subnetwork associated with fPC2 (all $p_{FWE-corrected} < .0001$). Connectivity between regions of this subnetwork containing bilateral posterior cingulate regions, bilateral parietal regions, medial, bilateral superior temporal sulcus, left temporal pole, and right medial polar prefrontal regions was positively associated with reduced fPC2. Connectivity was decreased in bilateral pregenual ACC regions, bilateral inferior temporal regions, left polar prefrontal medial regions, left posterior cingulate regions, and left hippocampal and parahippocampal regions.

For the CON, we used TFNBS to identify 1 subnetwork associated with fPC2 scores (all $p_{FWE-corrected} < .0001$). Connectivity between regions of this subnetwork was positively associated with reduced fPC2 for bilateral dACC, left insular regions, and right frontal superior regions. Connectivity was reduced for the left dACC, the dorsal medial region, and the anterolateral regions, right fronto-opercular cortices, and inferior parietal lobule.

For the FPN, we used TFNBS to identify 1 subnetwork associated with fPC2 (all $p_{FWE-corrected} < .0001$). Connectivity between regions of this subnetwork was positively associated with reduced fPC2 for bilateral precuneus regions and left lateropolar and DLPFC regions. Connectivity was reduced bilaterally in the anterior, lateral, prefrontal, superior parietal, and right parahippocampal cortices.

Association Between Motor Activity and Structural Connectivity

There were no significant associations between DTI or NODDI metrics along the tracts and fPC1 or fPC2 after adjustment for the number of tracts ([Table 3](#)). Results uncorrected for the number of tracts are reported in the [Supplement](#).

Table 2. Associations Between PC Scores and Apathy

Apathy Measure	fPC1		fPC2		fPC3		fPC4	
	z Value	p Value	z Value	p Value	z Value	p Value	z Value	p Value
AES	-3.37 ^a	.002	-1	.3	1	.3	0.2	.2
AMI	-1.89	.07	-2.53 ^a	.016	0.78	.4	-2.1	.04
DCA	-2.5	.018	-1.9	.07	-0.7	.48	-2.1	.04

AES, Apathy Evaluation Scale; AMI, Apathy Motivation Index; DCA, diagnostic criteria for apathy; fPC, functional principal component.

^aStatistically significant associations between fPCs and apathy measures. To be considered statistically significant, p value had to be $< .017$ (.05/3) to correct for the number of apathy variables tested.

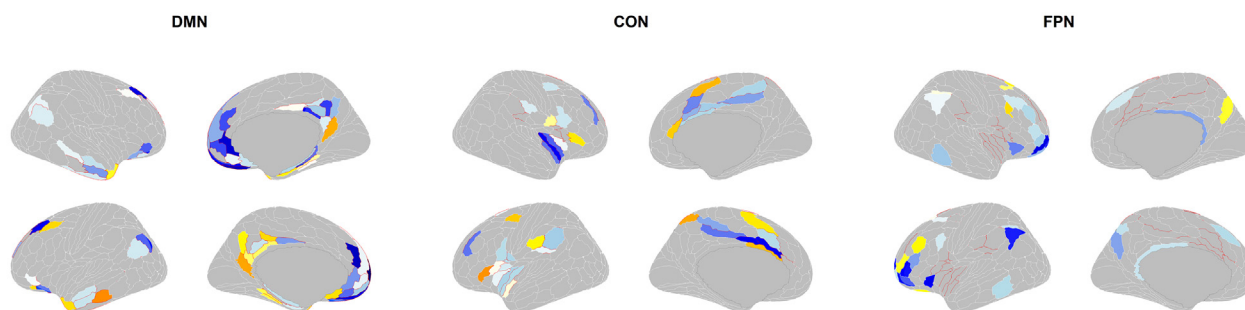
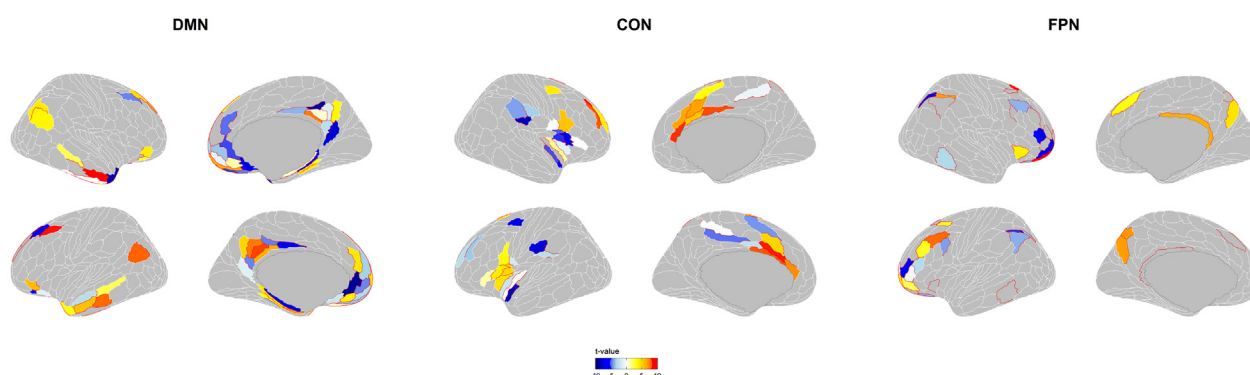
A Associations between brain functional connectivity and reduced fPC1**B** Associations between brain functional connectivity and reduced fPC2

Figure 2. Brain subnetworks associated with reduced scores of principal components (PCs) of motor activity in late-life depression. **(A)** Brain regions whose connectivity was significantly associated with scores of the first functional PC (fPC1), detected by threshold-free network-based statistics. Estimated marginal effects of each region of interest 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 was significantly associated with scores on the second fPC (fPC2) detected by threshold-free network-based statistics. Estimated marginal effects of each region of interest are reported to interpret the direction of the association when scores of fPC2 are reduced, i.e., when apathy severity increases. CON, cingulo-opercular network; DMN, default mode network; FPN, frontoparietal network.

DISCUSSION

We investigated the interplay between apathy, actimetry, and MRI-derived functional and structural connectivity in LLD. Our primary findings indicate that 2 patterns of motor activity were significantly associated with apathy. Reduced motor activity was associated with reduced connectivity within the DMN, CON, and FPN, while late chronotype was associated with more heterogeneous connectivity between both hemispheres in the same regions. There were no significant associations between microstructural metrics of white matter and patterns of motor activity. These 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 Were Associated With Apathy

We found that apathy severity was associated with reduced mean activity while low AMI scores were associated with late chronotype in LLD. The 2 patterns of activity were robustly found in the general adult population, notably in older adults

(42,43), as well as in patients with bipolar depression (44) and Alzheimer's disease (45). The relationship between decreased mean activity and the severity of apathy in LLD is consistent with that reported in apathy in Alzheimer disease (11), poor health (42) and increased depression symptoms in the general population (43), and bipolar disorder. Mean activity is also predictive of dysexecutive function (43) and mortality (42,43) in old age, thereby confirming its potential predictive utility in LLD. The pattern of activity characterized by late morning and late sleep suggests that the individuals' chronotypes were captured (46). In depression, the late chronotype has been associated with elevated depression severity (47,48), cognitive complaints (49), and risk of depressive episodes (50), putatively by a deficit in emotion regulation (51,52). The association between the late chronotype and AMI but not AES suggests that this pattern of activity may be specific to social apathy. This supports previous findings that link the late chronotype with reduced social activity in the general population (42). However, the early chronotype was associated with informant-rated scores of apathy in Alzheimer's disease or cognitive decline in older adults (43,53). Because the AMI is a self-report questionnaire that measures distinct subtypes of apathy (14),

Table 3. Associations Between Diffusion MRI Metrics and First Principal Component of Motor Activity by Tract

Tract	DTI				NODDI			
	FA		MD		ODI		Partial Volume	
	Corr. Coef.	Min. Cluster Size FWE	Corr. Coef.	Min. Cluster Size FWE	Corr. Coef.	Min. Cluster Size FWE	Corr. Coef.	Min. Cluster Size FWE
AC	0.51	35	0.61	58	0.47	31	0.54	33
CC_1	-0.34	35	0.38	58	-0.32	31	-0.25	33
CC_2	-0.45	35	0.42	58	-0.49	31	0.45	33
CC_3	-0.33	35	-0.18	58	-0.41	31	-0.38	33
CC_4	-0.36	35	0.15	58	-0.35	31	0.35	33
CC_5	-0.28	35	0.50	58	-0.30	31	0.49	33
CC_6	-0.34	35	0.30	58	-0.53	31	0.36	33
CC_7	-0.27	35	-0.38	58	-0.37	31	0.39	33
CG_left	-0.44	35	0.59	58	-0.34	31	0.31	33
CG_right	-0.37	35	0.43	58	-0.36	31	0.24	33
CST_left	-0.34	35	0.47	58	-0.37	31	0.43	33
CST_right	-0.33	35	0.32	58	0.29	31	0.41	33
ILF_left	-0.31	35	0.29	58	-0.34	31	0.30	33
ILF_right	-0.35	35	0.44	58	-0.45	31	0.38	33
SLF_I_left	-0.29	35	0.49	58	-0.35	31	0.35	33
SLF_I_right	-0.32	35	0.31	58	-0.40	31	0.35	33
SLF_II_left	-0.30	35	0.39	58	0.32	31	0.42	33
SLF_II_right	-0.40	35	0.39	58	-0.31	31	0.27	33
SLF_III_left	-0.52	35	0.39	58	0.36	31	0.39	33
SLF_III_right	-0.45	35	0.36	58	-0.30	31	0.30	33
UF_left	-0.38	35	0.22	58	-0.41	31	-0.33	33
UF_right	-0.34	35	0.31	58	-0.39	31	0.32	33

Along each white matter tract, significant clusters of metrics associated with fPC1 had to be greater than the familywise error rate cluster size, for a *p* value of .05. No clusters were statistically significant.

AC, anterior commissure; CC, corpus callosum; CG, cingulum; Corr. Coef., Pearson correlation coefficient; CST, corticospinal tract; DTI, diffusion tensor imaging; FA, fractional anisotropy; FWE, familywise error; ILF, inferior longitudinal fascicle; MD, mean diffusivity; Min, minimum; NODDI, neurite orientation dispersion and density imaging; ODI, orientation dispersion index; SLF, superior longitudinal fascicle; UF, uncinate fascicle.

lower scores may be associated with higher self-recognition of social impairment induced by depression than by cognitive deficits.

Within-Resting-State Network 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 LLD.

The DMN is central in depression pathogenesis (54,55). Sedentary motor behavior is correlated with reduced connectivity of the DMN in old (56) and younger adults (57), particularly between the ventromedial regions of the DMN (52). Hippocampal and parahippocampal volumes were also found to be associated with physical activity in healthy older adults (58–60) and vascular mild cognitive impairment (61). Therefore, sedentary behavior resulting from apathy may contribute to the persistence of depression and increase the risk of dementia (3,7) by exacerbating dysfunctions in the DMN that are associated with LLD.

The CON was positively associated with mean activity, confirming previous findings in older adults (56). More specifically, increased connectivity between the dACC, anterior insula, and supplementary motor area were predictive of sedentary behaviors in old age (62). However, key regions

implicated in motor cognitive control showed a negative association with mean activity; namely, dACC regions and bilateral fronto-opercular cortex. While one seed-based study found a positive association between dACC and motor activity in vascular mild cognitive impairment (63), the choice of the seed might have limited detection of a heterogeneous effect across dACC subregions, contrary to the Glasser's atlas (30).

Regarding the FPN, we found a global positive association between rsFC and mean motor activity and a reduced rsFC in the left DLPFC. As reported in healthy older adults (64,65), these regions are involved in motor planning and cognitive control (66,67), with their activation during executive function tasks being moderated by physical activity. Therefore, mean motor activity may indirectly measure dysexecutive syndrome, which is considered central in LLD and apathy development (68,69).

Within-Resting-State Network Connectivity Associated With Diurnal Chronotype

The diurnal chronotype was associated with heterogeneous rsFC between the left and right hemispheres in LLD compared with fPC1. DMN activity has been shown to be correlated with the late chronotype in healthy adults, with higher connectivity

between the precuneus and medial prefrontal cortex (70), while reduced connectivity between the posterior DMN (71) and the amygdala was found to mediate the association between the late chronotype and depression symptoms (72). Abnormal expression of genes regulating chronotypes had been reported in the ACC, the hippocampus, and the DLPFC in depression (73), suggesting that dysregulation of circadian rhythm is central in depression pathogenesis by disrupting DMN connectivity.

Regarding the CON, we found that late-chronotype participants had increased rsFC in the bilateral dACC and modified connectivity between the insula, supramarginal gyrus, and supplementary motor areas. In depression, the late chronotype has been associated with impaired functional activity of the supramarginal cortex and superior orbitofrontal regions (74) and reduced rsFC between the dACC and the amygdala (75). These changes in CON connectivity related to chronotype may be indicative of the modulating effect of circadian rhythm on reward processing (76) in apathy in LLD because reduced dACC activity was reported in late-chronotype participants during a monetary reward paradigm (77,78).

For the FPN, we found an association between the late chronotype and DLPFC, precuneus, and superior parietal cortex connectivity. The rsFC between the DLPFC and the cuneus has been found to mediate the impact of the late chronotype on subclinical depressive symptoms in adults (79). Reduced expression of circadian-regulating genes in the DLPFC has been reported in depression compared with healthy control participants (73,80). The modified connectivity in the FPN, as in the DMN, may be closely related to circadian rhythm dysregulation, which contributes to depression severity.

Absence of Association Between Patterns of Motor Activity and White Matter Connectivity

We did not find any significant associations between DTI or NODDI metrics and activity patterns, in contrast to our expectations based on the literature on LLD (81,82). DTI studies with older adults have found correlations between global FA and physical activity (83–86), as well as between physical activity and FA in the body of the corpus callosum or temporal areas (33,83,84). In adults, FA levels in the corpus callosum were associated with physical activity in bipolar disorder (85) and moderated the association between physical activity and working memory (86). All these studies combined tensor diffusion metrics with tract-based spatial statistics (87). While providing high statistical power, this method may suffer from a high false-positive rate, notably in regions of crossing pathways such as between the superior projections of the corpus callosum and the corona radiata fibers (88). The multicompartiment model that we used was meant to identify these tracts more precisely (89). However, correcting for multiple comparisons may have prevented us from reproducing the results from the aforementioned studies, these latter having focused on global brain or tract-specific metrics.

Limitations

Several limitations of the current study should be considered. Our study used a cross-sectional design with a recording

period of 3 days. While being the minimal period for acceptable estimation of motor activity (90,91), this short period may have prevented us from more robust assessment of participants' activity.

Moreover, PCA is subject to high variance and may not be exactly replicable across cohorts. Nevertheless, the top 2 fPCs are stable across studies (11,12,41–44), which can be explained by the fact that fPC1 summarizes the maximum total variance explained, i.e., the mean, while fPC2 is often related to the rate of change of motor activity over time. Nonetheless, PCA of motor activity alone may miss important aspects of apathy that qualitative behavioral description (92,93) or measures of underlying decision processes (94) could provide.

Furthermore, our sample size was relatively small. This may have limited our ability to detect a pattern of motor activity associated with functional impairment. The multiple comparisons performed in the study, particularly for white matter metrics across 22 bundles, further exacerbated this issue.

Finally, the inclusion of a control group in future studies will be important to validate the impact that LLD itself has on motor activity.

Conclusions

Our results provide new insights into the cerebral basis of apathy-related patterns of actimetry in LLD. We showed that these markers are more strongly associated with functional connectivity changes than the microstructure of white matter tracts. These results suggest that actimetry provides a measure of apathy related to brain functional dysconnectivity in networks related to goal-directed behaviors. Improvement in recruiting patients with LLD without criteria for significant apathy may increase between-group differences, especially for detecting microstructural white matter lesions.

ACKNOWLEDGMENTS AND DISCLOSURES

This study was supported by the Fondation de l'Avenir, Fondation Planiol, Fondation de France, and the Comité de recherche Clinique et d'Evaluation Thérapeutique from the Rennes University Hospital. J-CR and RH received financial support from the Institut de Neurosciences Clinique de Rennes.

We thank all the volunteers who participated in this study.

J-CR and RH were responsible for formal analysis. J-CR, RH, SD, JC, and GHR were responsible for methodology. J-CR, RH, SD, and JC were responsible for software. J-CR was responsible for visualization and writing the original draft of the manuscript. TD, IM-G, and LW were responsible for data curation. TD, DD, RD, and GHR were responsible for investigation. EB, LB, DD, J-MB, JC, and GHR were responsible for resources. EB, LB, J-MB, JC, and GHR were responsible for reviewing and editing the manuscript. DD, J-MB, and GHR were responsible for investigation. RD and GHR were responsible for funding acquisition. JC and GHR were responsible for conceptualization, supervision, and validation. All authors read and approved the final manuscript.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Centre Hospitalier Guillaume Rénier, Pôle Hospitalo-Universitaire de Psychiatrie Adulte, Rennes, France (J-CR, IM-G, LW, DD, J-MB, GHR); Centre d'Investigation Clinique 1414, Centre Hospitalier Universitaire de Rennes, Institut National de la Santé et de la Recherche Médicale (INSERM), Rennes, France (J-CR, DD, J-MB, GHR); Université de Rennes, Inria, Centre National de la Recherche Scientifique, IRISA, INSERM, Empenn U1228 ERL, Rennes, France (J-CR, RH, SD, EB, JC, GHR); CHU de Tours, Tours, France

(TD, LB); UMR 1253, iBrain, Université de Tours, INSERM, Tours, France (TD, LB); Centre d'Investigation Clinique 1415, CHU de Tours, INSERM, Tours, France (TD); CHU de Rennes, Service de Radiologie, Rennes, France (EB); Faculté de Médecine, Rennes Université, Rennes, France (DD, J-MB, GHR); and CHU de Nice, Université Côte d'Azur, Nice, France (RD).

JC and GHR contributed equally to this work.

Address correspondence to Jean-Charles Roy, M.D., Ph.D., at jc.roy@ch-guillaumeregnyier.fr.

Received Dec 28, 2023; revised Mar 4, 2024; accepted Apr 4, 2024.

Supplementary material cited in this article is available online at <https://doi.org/10.1016/j.bpsc.2024.04.002>.

REFERENCES

- Zhao Y, Wu X, Tang M, Shi L, Gong S, Mei X, *et al.* (2023): Late-life depression: Epidemiology, phenotype, pathogenesis and treatment before and during the COVID-19 pandemic. *Front Psychiatry* 14: 1017203.
- Zivin K, Wharton T, Rostant O (2013): The economic, public health, and caregiver burden of late-life depression. *Psychiatr Clin North Am* 36:631–649.
- Yuen GS, Bhutani S, Lucas BJ, Gunning FM, AbdelMalak B, Seirup JK, *et al.* (2015): Apathy in late-life depression: Common, persistent, and disabling. *Am J Geriatr Psychiatry* 23:488–494.
- Steffens DC, Fahed M, Manning KJ, Wang L (2022): The neurobiology of apathy in depression and neurocognitive impairment in older adults: A review of epidemiological, clinical, neuropsychological and biological research. *Transl Psychiatry* 12:525.
- Groeneweg-Koolhoven I, Comijs HC, Naarding P, de Waal MWM, van der Mast RC (2016): Apathy in older persons with depression: Course and predictors: The NESDO study. *J Geriatr Psychiatry Neurol* 29:178–186.
- Solomonov N, Victoria LW, Dunlop K, Respino M, Hoptman MJ, Zilcha-Mano S, *et al.* (2020): Resting state functional connectivity and outcomes of psychotherapies for late-life depression. *Am J Geriatr Psychiatry* 28:859–868.
- van Dalen JW, van Wanrooij LL, Moll van Charante EP, Brayne C, van Gool WA, Richard E (2018): Association of apathy with risk of incident dementia: A systematic review and meta-analysis. *JAMA Psychiatry* 75:1012–1021.
- Levy R, Dubois B (2006): Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex* 16:916–928.
- Robert P, Lanctôt KL, Agüera-Ortiz L, Aalten P, Bremond F, Defrancesco M, *et al.* (2018): Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *Eur Psychiatry* 54:71–76.
- Guercio BJ, Donovan NJ, Munro CE, Aghjayan SL, Wigman SE, Locascio JJ, *et al.* (2015): The apathy evaluation scale: A comparison of subject, informant, and clinician report in cognitively normal elderly and mild cognitive impairment. *J Alzheimers Dis* 47:421–432.
- Dickson SS, Husain M (2022): Are there distinct dimensions of apathy? The argument for reappraisal. *Cortex* 149:246–256.
- Husain M, Roiser JP (2018): Neuroscience of apathy and anhedonia: A transdiagnostic approach. *Nat Rev Neurosci* 19:470–484.
- Marin RS, Biedrzycki RC, Firinciogullari S (1991): Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res* 38:143–162.
- Ang YS, Lockwood P, Apps MAJ, Muhammed K, Husain M (2017): Distinct subtypes of apathy revealed by the apathy motivation index. *PLoS One* 12:e0169938.
- Roy JC, Desmidt T, Dam S, Mirea-Grivel I, Weyl L, Banner E, *et al.* (2023): Connectivity patterns of the core resting-state networks associated with apathy in late-life depression. *J Psychiatry Neurosci* 48:E404–E413.
- Alexopoulos GS, Hoptman MJ, Yuen G, Kanellopoulos D, Seirup JK, Lim KO, Gunning FM (2013): Functional connectivity in apathy of late-life depression: A preliminary study. *J Affect Disord* 149:398–405.
- Robert G, Banner E, Comte M, Domain L, Corouge I, Dondaine T, *et al.* (2021): Multimodal brain imaging connectivity analyses of emotional and motivational deficits in depression among women. *J Psychiatry Neurosci* 46:E303–E312.
- Yuen GS, Gunning-Dixon FM, Hoptman MJ, AbdelMalak B, McGovern AR, Seirup JK, Alexopoulos GS (2014): The salience network in the apathy of late-life depression. *Int J Geriatr Psychiatry* 29:1116–1124.
- Oberlin LE, Respino M, Victoria L, Abreu L, Hoptman MJ, Alexopoulos GS, Gunning FM (2022): Late-life depression accentuates cognitive weaknesses in older adults with small vessel disease. *Neuropsychopharmacology* 47:580–587.
- Gandelman JA, Albert K, Boyd BD, Park JW, Riddle M, Woodward ND, *et al.* (2019): Intrinsic functional network connectivity is associated with clinical symptoms and cognition in late-life depression. *Biol Psychiatry Cogn Neurosci Neuroimaging* 4:160–170.
- Coloigner J, Batail JM, Commowick O, Corouge I, Robert G, Barillot C, Drapier D (2019): White matter abnormalities in depression: A categorical and phenotypic diffusion MRI study. *NeuroImage Clin* 22: 101710.
- Montgomery SA, Asberg M (1979): A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134:382–389.
- Nelson HE (1976): A modified card sorting test sensitive to frontal lobe defects. *Cortex* 12:313–324.
- Reitan RM (1958): Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills* 8:271–276.
- Golden C, Freshwater SM, Golden Z (2002): Stroop Color and Word Test [Database record]. APA PsycTests. Available at: <https://doi.org/10.1037/t06065-000>.
- Cardebat D, Doyon B, Puel M, Goulet P, Joannette Y (1990): [Formal and semantic lexical evocation in normal subjects. Performance and dynamics of production as a function of sex, age and educational level]. *Acta Neurol Belg* 90:207–217.
- Scherrer B, Warfield SK (2012): Parametric representation of multiple white matter fascicles from Cube and sphere diffusion MRI. *PLoS One* 7:e48232.
- Ramsay J, Silverman BW (2005): *Functional Data Analysis*. New York, NY: Springer Science and Business Media.
- Glasser MF, Coalson TS, Robinson EC, Hacker CD, Harwell J, Yacoub E, *et al.* (2016): A multi-modal parcellation of human cerebral cortex. *Nature* 536:171–178.
- Ji JL, Spronk M, Kulkarni K, Repovš G, Anticevic A, Cole MW (2019): Mapping the human brain's cortical-subcortical functional network organization. *Neuroimage* 185:35–57.
- Wasserthal J, Neher P, Maier-Hein KH (2018): TractSeg – Fast and accurate white matter tract segmentation. *Neuroimage* 183:239–253.
- Kim BR, Kwon H, Chun MY, Park KD, Lim SM, Jeong JH, Kim GH (2020): White matter integrity is associated with the amount of physical activity in older adults with super-aging. *Front Aging Neurosci* 12:549983.
- Wen MC, Steffens DC, Chen MK, Zainal NH (2014): Diffusion tensor imaging studies in late-life depression: Systematic review and meta-analysis. *Int J Geriatr Psychiatry* 29:1173–1184.
- Le Heron C, Apps MAJ, Husain M (2018): The anatomy of apathy: A neurocognitive framework for amotivated behaviour. *Neuropsychologia* 118:54–67.
- Soares JM, Marques P, Alves V, Sousa N (2013): A hitchhiker's guide to diffusion tensor imaging. *Front Neurosci* 7:31.
- Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC (2012): NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. *NeuroImage* 61:1000–1016.
- Zalesky A, Fornito A, Bullmore ET (2010): Network-based statistic: Identifying differences in brain networks. *Neuroimage* 53:1197–1207.
- Baggio HC, Abos A, Segura B, Campabadal A, Garcia-Diaz A, Uribe C, *et al.* (2018): Statistical inference in brain graphs using threshold-free network-based statistics. *Hum Brain Mapp* 39:2289–2302.
- Searle SR, Speed FM, Milliken GA (1980): Population marginal means in the linear model: An alternative to least squares means. *Am Stat* 34:216–221.
- Wasserthal J, Maier-Hein KH, Neher PF, Northoff G, Kubera KM, Fritze S, *et al.* (2020): Multiparametric mapping of white matter microstructure in catatonia. *Neuropsychopharmacology* 45:1750–1757.
- Nichols TE, Holmes AP (2002): Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Hum Brain Mapp* 15:1–25.

42. Stein MJ, Baurecht H, Sedlmeier AM, Konzok J, Bohmann P, Fontvieille E, *et al.* (2023): Association between circadian physical activity patterns and mortality in the UK Biobank. *Int J Behav Nutr Phys Act* 20:102.
43. Zeitzer JM, Blackwell T, Hoffman AR, Cummings S, Ancoli-Israel S, Stone K, Osteoporotic Fractures in Men (MrOS) Study Research Group (2018): Daily patterns of accelerometer activity predict changes in sleep, cognition, and mortality in older men. *J Gerontol A Biol Sci Med Sci* 73:682–687.
44. Gershon A, Ram N, Johnson SL, Harvey AG, Zeitzer JM (2016): Daily actigraphy profiles distinguish depressive and interepisode states in bipolar disorder. *Clin Psychol Sci* 4:641–650.
45. Zeitzer JM, David R, Friedman L, Mullin E, Garcia R, Wang J, *et al.* (2013): Phenotyping apathy in individuals with Alzheimer disease using functional principal component analysis. *Am J Geriatr Psychiatry* 21:391–397.
46. Adan A, Archer SN, Hidalgo MP, Di Milia L, Natale V, Randler C (2012): Circadian typology: A comprehensive review. *Chronobiol Int* 29:1153–1175.
47. Müller MJ, Kundermann B, Cabanel N (2016): Eveningness and poor sleep quality independently contribute to self-reported depression severity in psychiatric inpatients with affective disorder. *Nord J Psychiatry* 70:329–334.
48. Müller MJ, Cabanel N, Olschinski C, Jochim D, Kundermann B (2015): Chronotypes in patients with nonseasonal depressive disorder: Distribution, stability and association with clinical variables. *Chronobiol Int* 32:1343–1351.
49. Coleman MY, Cain SW (2019): Eveningness is associated with greater subjective cognitive impairment in individuals with self-reported symptoms of unipolar depression. *J Affect Disord* 256:404–415.
50. Chan JWY, Lam SP, Li SX, Yu MWM, Chan NY, Zhang J, Wing YK (2014): Eveningness and insomnia: Independent risk factors of non-remission in major depressive disorder. *Sleep* 37:911–917.
51. Van den Berg JF, Kivelä L, Antypa N (2018): Chronotype and depressive symptoms in students: An investigation of possible mechanisms. *Chronobiol Int* 35:1248–1261.
52. Watts AL, Norbury R (2017): Reduced effective emotion regulation in night owls. *J Biol Rhythms* 32:369–375.
53. Alfini A, Albert M, Faria AV, Soldan A, Pettigrew C, Wanigatunga S, *et al.* (2021): Associations of actigraphic sleep and circadian rest/activity rhythms with cognition in the early phase of Alzheimer's disease. *Sleep Adv* 2:zpab007.
54. Zhou HX, Chen X, Shen YQ, Li L, Chen NX, Zhu ZC, *et al.* (2020): Rumination and the default mode network: Meta-analysis of brain imaging studies and implications for depression. *Neuroimage* 206:116287.
55. Martins B, Mather M (2016): Default mode network and later-life emotion regulation: Linking functional connectivity patterns and emotional outcomes. In: *Emotion, Aging, and Health*. Washington, DC: American Psychological Association, 9–29.
56. Dion C, Tanner JJ, Crowley SJ, Wiggins ME, Mareci T, Ding M, *et al.* (2021): Functional connectivity of key resting state networks and objectively measured physical activity in older adults with joint pain: A pilot study. *Exp Gerontol* 153:111470.
57. Cascio CN, O'Donnell MB, Tinney FJ, Lieberman MD, Taylor SE, Strecher VJ, Falk EB (2016): Self-affirmation activates brain systems associated with self-related processing and reward and is reinforced by future orientation. *Soc Cogn Affect Neurosci* 11:621–629.
58. Domingos C, Picó-Pérez M, Magalhães R, Moreira M, Sousa N, Pêgo JM, Santos NC (2021): Free-living physical activity measured with a wearable device is associated with larger hippocampus volume and greater functional connectivity in healthy older adults: An observational, cross-sectional study in Northern Portugal. *Front Aging Neurosci* 13:729060.
59. Varma VR, Chuang YF, Harris GC, Tan EJ, Carlson MC (2015): Low-intensity daily walking activity is associated with hippocampal volume in older adults. *Hippocampus* 25:605–615.
60. Machida M, Takamiya T, Amagasa S, Murayama H, Fujiwara T, Odagiri Y, *et al.* (2022): Objectively measured intensity-specific physical activity and hippocampal volume among community-dwelling older adults. *J Epidemiol* 32:489–495.
61. Li H, Sun D, Lu D, Zhang J, Zeng J (2020): Low hippocampal dentate gyrus volume associated with hypertension-related cognitive impairment. *Am J Alzheimers Dis Other Demen* 35:1533317520949782.
62. Morris TP, Kucyi A, Anteraper SA, Geddes MR, Nieto-Castañón A, Burzynska A, *et al.* (2022): Resting state functional connectivity provides mechanistic predictions of future changes in sedentary behavior. *Sci Rep* 12:940.
63. Chang YT, Liu CT, Hsu SW, Lee CC, Huang PC (2022): Functional connectivity, physical activity, and neurocognitive performances in patients with vascular cognitive impairment, no dementia. *Curr Alzheimer Res* 19:56–67.
64. Kimura K, Yasunaga A, Wang LQ (2013): Correlation between moderate daily physical activity and neurocognitive variability in healthy elderly people. *Arch Gerontol Geriatr* 56:109–117.
65. Balbim GM, Ajilore OA, Erickson KI, Lamar M, Aguiñaga S, Bustamante EE, Marquez DX (2021): The impact of the BAILAMOS™ dance program on brain functional connectivity and cognition in older latino adults: A pilot study. *J Cogn Enhanc* 5:1–14.
66. Nitschke K, Köstering L, Finkel L, Weiller C, Kaller CP (2017): A meta-analysis on the neural basis of planning: Activation likelihood estimation of functional brain imaging results in the Tower of London task. *Hum Brain Mapp* 38:396–413.
67. Petrides M (2005): Lateral prefrontal cortex: Architectonic and functional organization. *Philos Trans R Soc Lond B Biol Sci* 360:781–795.
68. Lockwood KA, Alexopoulos GS, van Gorp WG (2002): Executive dysfunction in geriatric depression. *Am J Psychiatry* 159:1119–1126.
69. Alexopoulos GS (2001): "The depression-executive dysfunction syndrome of late life": A specific target for D3 agonists? *Am J Geriatr Psychiatry* 9:22–29.
70. Tian Y, Chen X, Xu D, Yu J, Lei X (2020): Connectivity within the default mode network mediates the association between chronotype and sleep quality. *J Sleep Res* 29:e12948.
71. Horne CM, Norbury R (2018): Altered resting-state connectivity within default mode network associated with late chronotype. *J Psychiatr Res* 102:223–229.
72. Smagula SF, Karim HT, Ibrahim TS, Krafty RT, Stahl ST, Rodakowski J, *et al.* (2021): Resting-state function connectivity associated with being a "morning-type" dementia caregiver and having lower depression symptom severity. *J Gerontol B Psychol Sci Soc Sci* 76:1071–1076.
73. Li JZ, Bunney BG, Meng F, Hagenauer MH, Walsh DM, Vawter MP, *et al.* (2013): Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. *Proc Natl Acad Sci U S A* 110:9950–9955.
74. Chen Z, Zhao S, Tian S, Yan R, Wang H, Wang X, *et al.* (2022): Diurnal mood variation symptoms in major depressive disorder associated with evening chronotype: Evidence from a neuroimaging study. *J Affect Disord* 298:151–159.
75. Horne CM, Norbury R (2018): Late chronotype is associated with enhanced amygdala reactivity and reduced fronto-limbic functional connectivity to fearful versus happy facial expressions. *NeuroImage* 171:355–363.
76. Byrne JEM, Tremain H, Leitan ND, Keating C, Johnson SL, Murray G (2019): Circadian modulation of human reward function: Is there an evidentiary signal in existing neuroimaging studies? *Neurosci Biobehav Rev* 99:251–274.
77. Hasler BP, Casement MD, Sitnick SL, Shaw DS, Forbes EE (2017): Eveningness among late adolescent males predicts neural reactivity to reward and alcohol dependence 2 years later. *Behav Brain Res* 327:112–120.
78. Hasler BP, Clark DB (2013): Circadian misalignment, reward-related brain function, and adolescent alcohol involvement. *Alcohol Clin Exp Res* 37:558–565.
79. Jia Y, Tian Y, Wang H, Lei X (2023): Functional connectivity from dorsolateral prefrontal cortex mediates the impact of social jetlag on depressive tendency in young adults. *Chronobiol Int* 40:824–833.

Activity and Brain Connectivity in Late-Life Depression

80. Edgar N, McClung CA (2013): Major depressive disorder: A loss of circadian synchrony? *BioEssays* 35:940–944.
81. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlon M (1997): “Vascular depression” hypothesis. *Arch Gen Psychiatry* 54:915–922.
82. Sheline YI, Price JL, Vaishnavi SN, Mintun MA, Barch DM, Epstein AA, *et al.* (2008): Regional white matter hyperintensity burden in automated segmentation distinguishes late-life depressed subjects from comparison subjects matched for vascular risk factors. *Am J Psychiatry* 165:524–532.
83. Tian Q, Glynn NW, Erickson KI, Aizenstein HJ, Simonsick EM, Yaffe K, *et al.* (2015): Objective measures of physical activity, white matter integrity and cognitive status in adults over age 80. *Behav Brain Res* 284:51–57.
84. Burzynska AZ, Jiao Y, Knecht AM, Fanning J, Awick EA, Chen T, *et al.* (2017): White matter integrity declined over 6-months, but dance intervention improved integrity of the fornix of older adults. *Front Aging Neurosci* 9:59.
85. Verkooijen S, Stevelink R, Abramovic L, Vinkers CH, Ophoff RA, Kahn RS, *et al.* (2017): The association of sleep and physical activity with integrity of white matter microstructure in bipolar disorder patients and healthy controls. *Psychiatry Res Neuroimaging* 262:71–80.
86. Bracht T, Steinau S, Federspiel A, Schneider C, Wiest R, Walther S (2018): Physical activity is associated with left corticospinal tract microstructure in bipolar depression. *NeuroImage Clin* 20:939–945.
87. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, *et al.* (2006): Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31:1487–1505.
88. Bach M, Laun FB, Leemans A, Tax CMW, Biessels GJ, Stieltjes B, Maier-Hein KH (2014): Methodological considerations on tract-based spatial statistics (TBSS). *Neuroimage* 100:358–369.
89. Kamiya K, Hori M, Aoki S (2020): NODDI in clinical research. *J Neurosci Methods* 346:108908.
90. Littner M, Kushida CA, Anderson WM, Bailey D, Berry RB, Davila DG, *et al.* (2003): Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: An update for 2002. *Sleep* 26:337–341.
91. Sasaki JE, Júnior JH, Meneguci J, Tribess S, Marocolo Júnior M, Stabelini Neto A, Virtuoso Júnior JS (2018): Number of days required for reliably estimating physical activity and sedentary behaviour from accelerometer data in older adults. *J Sports Sci* 36:1572–1577.
92. König A, Aalten P, Verhey F, Bensadoun G, Petit PD, Robert P, David R (2014): A review of current information and communication technologies: Can they be used to assess apathy? *Int J Geriatr Psychiatry* 29:345–358.
93. Peltier C, Lejeune FX, Jorgensen LGT, Rametti-Lacroux A, Tanguy D, Godefroy V, *et al.* (2022): A temporal classification method based on behavior time series data in patients with behavioral variant of frontotemporal dementia and apathy. *J Neurosci Methods* 376:109625.
94. Pessiglione M, Vinckier F, Bouret S, Daunizeau J, Le Bouc R (2018): Why not try harder? Computational approach to motivation deficits in neuro-psychiatric diseases. *Brain* 141:629–650.