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The body of evidence of late-life depression: the complex relationship between depressive symptoms, movement, dyspnea and cognition

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ABSTRACT

Background: Physical symptoms play an important role in late-life depression and may contribute to residual symptomatology after antidepressant treatment. In this exploratory study, we examined the role of specific bodily dimensions including movement, respiratory functions, fear of falling, cognition, and physical weakness in older people with depression.

Methods: Clinically stable older patients with major depression within a Psychiatric Consultation-Liaison program for Primary Care underwent comprehensive assessment of depressive symptoms, instrumental movement analysis, dyspnea, weakness, activity limitations, cognitive function, and fear of falling. Network analysis was performed to explore the unique adjusted associations between clinical dimensions.

Results: Sadness was associated with worse turning and walking ability and movement transitions from walking to sitting, as well as with worse general cognitive abilities. Sadness was also connected with dyspnea, while neurovegetative depressive burden was connected with activity limitations.

Discussion: Limitations of motor and cognitive function, dyspnea, and weakness may contribute to the persistence of residual symptoms of late-life depression.

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Introduction

The reciprocal interactions between mental and physical symptoms and signs are particularly relevant factors in shaping the clinical presentation and pathophysiology of depression in old age. Clarifying these complex, multifaceted relationships may improve our knowledge on late-life depression residual symptoms and therapeutic approaches.

Late-life depression defies the attempt to set clear boundaries between the mind and body (Alexopoulos, 2019). Even at a young age, the clinical picture of depression includes physical signs and symptoms that reciprocally contribute to eliciting psychological reactions and maintaining a state of low mood (Fried, Epskamp, Nesse, Tuerlinckx, & Borsboom, 2016). Later, the age-dependent loss of physical and cognitive performance progressively increases the vulnerability toward depression. Late-life depression often arises due to physical diseases typical of late adulthood and often creates vicious cycles of increased disability (Belvederi Murri et al., 2020; Gleason, Pierce, Walker, & Warnock, 2013; Hegeman et al., 2017; Triolo et al., 2020). In old age, physical manifestations of depression become even more prominent and are often difficult to disentangle from symptoms of somatic diseases (Hegeman, Kok, Van Der Mast, & Giltay, 2012). Overall, age-related physical changes and somatic symptoms act as important drivers of depression clinical course, with known reciprocal interactions underpinned by multiple behavioral, psychological, and biological mechanisms (Hegeman et al., 2017; Laird, Krause, Funes, & Lavretsky, 2019; Triolo et al., 2020). Such a complex picture may partly explain why treating depression with antidepressant drugs is only partly effective in old age: patients are often left with significant residual depressive symptoms, the most frequent of which, not coincidentally, are somatic: tension, anxiety (Dombrovski et al., 2007), loss of energy and lassitude (Hybels, Steffens, McQuoid, & Krishnan, 2005).

Despite being key features, the contribution of bodily functions and symptoms to the clinical picture of late-life depression is often overlooked in the assessment and treatment. For instance, depression is associated with movement abnormalities, which dramatically increase disability and Fear of Falling (FOF), ultimately favoring the persistence of depression (Denkinger, Lukas, Nikolaus, & Hauer, 2015). Only a few studies of late-life depression have considered the specific role of movement abilities in the clinical picture. Movement abnormalities are usually measured with a few questionnaire items on psychomotor retardation or agitation (Belvederi Murri et al., 2020). This approach fails to capture important features of movement, as well as the effect of other concurrent factors that increase disability by affecting movement, such as musculoskeletal diseases or executive functions. Another important yet often overlooked aspect of depression is dyspnea: it is reciprocally linked with symptoms of anxiety in patients with physical illnesses (Trevisan et al., 2020; Yohannes et al., 2022).

Investigating the relationship between movement, dyspnea, and depressive symptoms among individuals with late-life depression may shed light on the mechanisms that contribute to the persistence of residual depressive symptoms, as well as offer a model for integrated management approaches (Yohannes & Alexopoulos, 2014). Network analyses seem particularly fit for investigating such bidirectional relationships simultaneously while accounting for potential confounders (Belvederi Murri, Amore, Respino, & Alexopoulos, 2018; Isvoranu et al., 2021). Thus, this exploratory study aimed to examine the relationship between bodily features (movement, dyspnea, weakness, fear

of falling, cognition, and comorbidities) and depressive symptoms in late-life depression, using network analysis. Based on prior literature, we hypothesized that measurements of physical slowing would be associated with core and neurovegetative depressive symptoms, while variables capturing abnormal movement kinematics would be related to physical comorbidities (Belvederi Murri et al., 2020). Furthermore, we expected that cognitive functions would be connected both with depressive symptoms and movement abilities (Belvederi Murri et al., 2020; Rojer et al., 2021). Lastly, we hypothesized that the severity of dyspnea would be associated with both depressive symptoms and fear of falling (Denkinger, Lukas, Nikolaus, & Hauer, 2015; Yohannes, Junkes-Cunha, Smith, & Vestbo, 2017).

Methods

Subjects

Recruitment was based on referrals from primary care physicians within a Psychiatric Consultation-Liaison Program for Primary Care located in Bologna, Italy. The program was further developed in a Community Mental Health Center to include specific activities and initiatives for older adults suffering from mood disorders. These included, among others, participation in a multi-centric study on physical exercise for depression and a rehabilitation program based on group psychotherapy and group physical rehabilitation.

This study is part of a project aimed at evaluating changes in mental and bodily parameters during a rehabilitation program for older individuals with depression. Participation was offered to individuals aged 65 or older diagnosed with non-psychotic, chronic recurrent major depression. Exclusion criteria were the presence of dementia or recent reacutization of physical illnesses (e.g., myocardial infarction), as well as recent hospitalizations for any cause within the previous 6 months. Participants were assessed in a phase of clinical stability at least 6 months after starting at least one trial of antidepressant drugs at standard dosage. All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board in Bologna.

Psychometric Assessments and Measures

Depressive symptoms were assessed with the Italian version of the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979). This clinician-rated questionnaire is used to rate the severity of 10 depressive symptoms on a scale from 0 to 6. Compared with other assessment tools, such as the Hamilton Depression Scale, the MADRS gives lower weight to somatic symptoms. Thus, it is considered more specific for use among older individuals with physical comorbidities.

Cognitive performance was assessed using the Italian version of the Montreal Cognitive Assessment (MoCA) (Pirani, Tulipani, & M, 2006; Santangelo et al., 2014). The MoCA is a screening instrument evaluating seven cognitive domains, namely visuospatial-executive, denomination, attention, fluency, abstraction, memory, and orientation. Usually, a cutoff score of 24 is used to differentiate normal cognitive functions from Mild Cognitive Impairment or dementia. MoCA scores, however, are generally lower among older individuals with major depression than in cognitively intact individuals (Blair et al., 2016).

Physical comorbidities were assessed with the Cumulative Illness Rating Scale (CIRS), a clinician-rated tool. The CIRS rates the severity of diseases across 14 categories of bodily systems on a scale from 0 (absent) to 4 (very severe) (Miller et al., 1992). The comorbidity index is derived as the count of diseases with a severity of 3 or higher (excluding the psychiatric category) and serves as a reliable index of disease burden (De Groot, Beckerman, Lankhorst, & Bouter, 2003).

Fear of falling was assessed using the Fall Efficacy Scale – International (FES-I), a 16-item self-report scale (Yardley et al., 2005). The FES-I inquires about the concern of falling while performing various activities of daily living on a scale from 1 (not at all concerned) to 4 (very concerned). Its total score ranges from 16 to 64, with scores above 28 indicating high concern of falling.

Dyspnea, physical weakness, and functional limitations were assessed with the self-report Pulmonary Functional Status & Dyspnea Questionnaire-Modified (PFSDQ-M) (Lareau, Meek, & Roos, 1998). The questionnaire investigates the severity and frequency of shortness of breath, fatigue, and impairment in daily activities. The questionnaire was originally developed to evaluate such dimensions among individuals with COPD, and asks responders to relate their level of functioning to the onset of breathing problems. Since not all participants in this study suffered from diagnosed respiratory diseases, we offered clarifications on the PFSDQ-M whenever required by participants. For the purpose of this study, mean scores of each domain's items were used as indices of activity impairment, dyspnea, and fatigue, respectively.

Instrumented Assessment of Movement

Movement was assessed with an Instrumented Timed Up and Go test (iTUG) (Coni, Mellone, Colpo, Bandinelli, & Chiari, 2018), an instrumented version of the TUG test (Podsiadlo & Richardson, 1991). The TUG test is traditionally used to assess mobility, balance, walking ability, and fall risk in older adults. A smartphone-based system with a custom application (mHealth Technologies, Italy) was used to record inertial signals from the smartphone embedded sensors and allowed to compute from these 37 features (Mellone, Tacconi, & Chiari, 2012). The features include the duration of the test subtasks (i.e. walk, turns, and postural transitions); the root mean square (RMS) and range of the signals; the normalized jerk of the walk; and the jerkiness of the postural transitions and the turns. During the test, the smartphone (SP) is worn on the lower back using a case waist belt.

Conceptual Model Computation

For the purpose of this study, data from the iTUG were analyzed using a recent factorial structure (Coni, Mellone, Colpo, Bandinelli, & Chiari, 2018). The exploratory factor analysis (EFA) was performed to reduce the dimension of the dataset and to uncover the underlying relationships between the instrumented measures. The computation of factors is based on two preliminary assumptions: (1) normally distributed data. Scores of jerk scores for all the sub-phases in antero-posterior (AP), medio-lateral (ML), and vertical (V) directions were not normally distributed; thus they were log-transformed, standardized to zero mean, and compared using z-scores; (2) the resulting factor structure should explain at least 70% of the total variance, to retain as much of the original information as possible.

Varimax rotation was used to derive orthogonal factor scores. A scree plot with parallel analysis was used to determine the minimum number of factors to retain. First, we verified that at least 70% of the total variance was explained. Second, we retained only instrumented measures with factor loading greater than 0.5 (absolute value). Finally, each factor was mapped onto a conceptual domain. We labeled conceptual domains based on the contributing sensor-based measures. The analysis and functional interpretation of functional meaning were based on our a priori knowledge of these instrumented measures.

Other Descriptive Variables

Self-reported sociodemographic and anthropometric information were collected for descriptive purposes: civil status, educational attainment (number of years of formal education), and body mass index (height/weight^2).

Data Analyses

We used a network approach to examine the relationship between depressive symptoms and symptoms related to bodily functions. Network analyses were based on multivariate Gaussian Graphical Models (GGMs). GGMs provide an estimate of the unique shared covariance between each couple of variables, after accounting for all other variables in the model (2706i">Borsboom et al., 2021). Variables are visualized as nodes connected by edges, which represent the strength of their unique association. The thickness of edges is proportional to the strength of the relationship, while their color indicates if the association is positive (green) or negative (red). Different estimation approaches exist: the *ggmModSelect* algorithm of the *qgraph* R package (Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012) displays a good trade-off between levels of specificity and sensitivity in the identification of significant edges from small samples and a high number of variables (Isvoranu & Epskamp, 2021). Briefly, the algorithm iteratively identifies multiple network structures by varying the tuning parameter of the Least Absolute Shrinkage and Selection Operator (LASSO) regularization procedure. At each step, the algorithm removes edges from the "full" graph, re-estimates the model without regularization and calculates the Bayesian Information Criteria fit index. The most significant edges in the graph are identified from the best fitting model and visualized. Furthermore, we report on node centrality (strength and expected influence) and predictability (R^2), two indices of node interconnectedness in the network.

Prior to network estimation, we performed data reduction of MADRS and MOCA rating scales, in order to avoid redundancy of items, while maintaining some level of specificity: multiple facets of depression present distinct associations with physical symptoms (Belvederi Murri et al., 2021); executive functions specifically influence movement. We used the Loadings Comparison Test (LCT) to guide the choice whether to use factor analysis or computing the scores of network communities ("symptom complexes"). The LCT estimates the likelihood that data is generated from a network or latent factor structure (Christensen & Golino, 2021b); this has direct implications for the grouping of items in clinical data (Belvederi Murri et al., 2021). In case of a latent factor structure, we would compute the score of latent factors, establishing their number with a parallel analysis. In case, of a network structure, we would use Exploratory Graph Analysis (EGA) with the

Walktrap algorithm to identify how variables were organized into communities, i.e. groups of highly interconnected nodes (Christensen & Golino, 2021a). In particular, we used the bootstrapped EGA function of the R EGAnet package (Golino & Christensen, 2020) with 1000 iterations to examine the stability of membership of nodes to communities. Network loadings would be then used to extract participants' scores for each community.

Results

Sample Characteristics

The study sample comprised 75 subjects. After the removal of missing data, complete data for 60 subjects were available. Participants' demographic and clinical characteristics are reported in Table 1. Participants were mostly male, married, with a mean age of 73 years.

Reduction of Data of Depressive Symptoms and Cognition

The analysis of MADRS item-level data with the LCT yielded a more probable Network structure (66% of the iterations). The bootstrapped EGA procedure identified a median of three communities (95% CI: 1.23–4.77) from a relatively sparse network (Figure S1). The communities were "*Anhedonia/lassitude*," "*Sadness*" and "*Neurovegetative/concentration*" (Table S1). Thus, using network loadings, we computed the scores of these three depressive symptom complexes for each subject for use in the general network.

Analysis of the MoCA data with the LCT suggested a more probable latent factor structure (91% of the iterations). Congruent with the relatively low sample size, parallel analysis indicated the presence of a single factor, whereby previous studies highlighted the presence of a bi-factorial structure (one general factor plus one or more specific factors) (Sala et al., 2019). In order to attempt to distinguish specific aspects of cognition (most

Table 1. Sociodemographic and clinical characteristics of the analytical sample.

Age, mean (SD)	73.031 (8.721)
Gender, Female, n (%)	22 (29.3%)
Civil status, n (%)	
single	10 (16.7%)
married	34 (56.7%)
widow	12 (20.0%)
separated	1 (1.7%)
divorced	3 (5.0%)
Education years; Mean (SD)	9.136 (4.718)
BMI; Mean (SD)	26.331 (3.759)
CIRS comorbidity; Mean (SD)	1.873 (2.278)
MoCA total score; Mean (SD)	22.367 (5.989)
MADRS total score; Mean (SD)	24.323 (9.271)
PFSDQ-M activity impairment; Mean (SD)	0.810 (1.143)
PFSDQ-M dyspnea; Mean (SD)	0.716 (1.051)
PFSDQ-M fatigue; Mean (SD)	0.579 (0.812)
FES-I total score; Mean (SD)	23.812 (7.972)

BMI: body mass index; CIRS: Cumulative Illness Rating Scale; MoCA: Montreal Cognitive Assessment; MADRS: Montgomery-Åsberg Depression Rating Scale; DPMSQ: Pulmonary Functional Status & Dyspnea Questionnaire-Modified; FES-I: Fall Efficacy Scale-International.

importantly executive functions), we chose to use a bi-factor model based on one general factor plus two specific factors, despite a slightly lower fit to data. Factor loadings and model comparisons are reported in the supplement (Table S2, Figure S2, and Table S3).

Conceptual Model Computation for Mobility Measures

The factor analysis grouped 35 out of 37 instrumented measures, accounting for 77% of the total variance. Scores of the following eight factors were derived for each subject: (1) 7 m Walking Ability; (2) 180T Turning Impairment; (3) Turn-to-Sit Jerkiness; (4) Turn-to-Sit Impairment; (5) Sit-to-Walk Jerkiness; (6) Sit-to-Walk weakness; (7) ML Turn-to-Sit weakness; (8) V Turn-to-Sit weakness. Higher factor scores indicate worse performance in the TUG except for factor 1, where higher scores indicate greater walking ability.

Associations Between Clinical Features: Unadjusted Correlations and Network Analysis

The exploration of bivariate unadjusted correlations confirmed the presence of multiple associations between depressive symptoms, movement, and other clinical features (Figure 1; Figure S3). All depressive symptom complexes positively

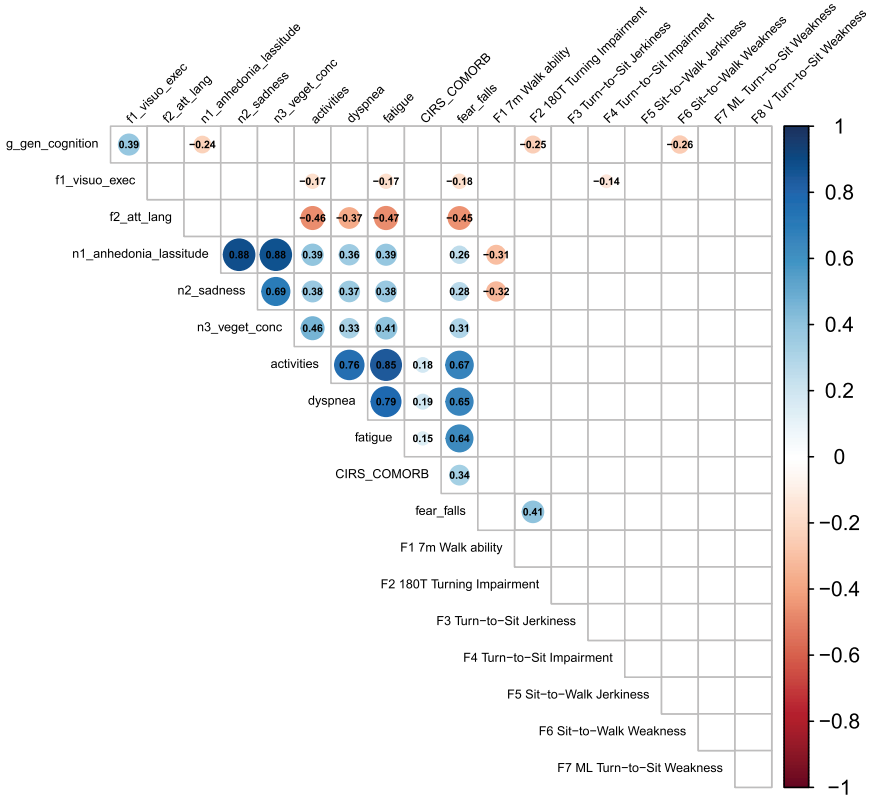

Figure 1. Bivariate correlations between depressive symptoms and other variables. Spearman rho for significant correlations ($p < .05$) are reported.

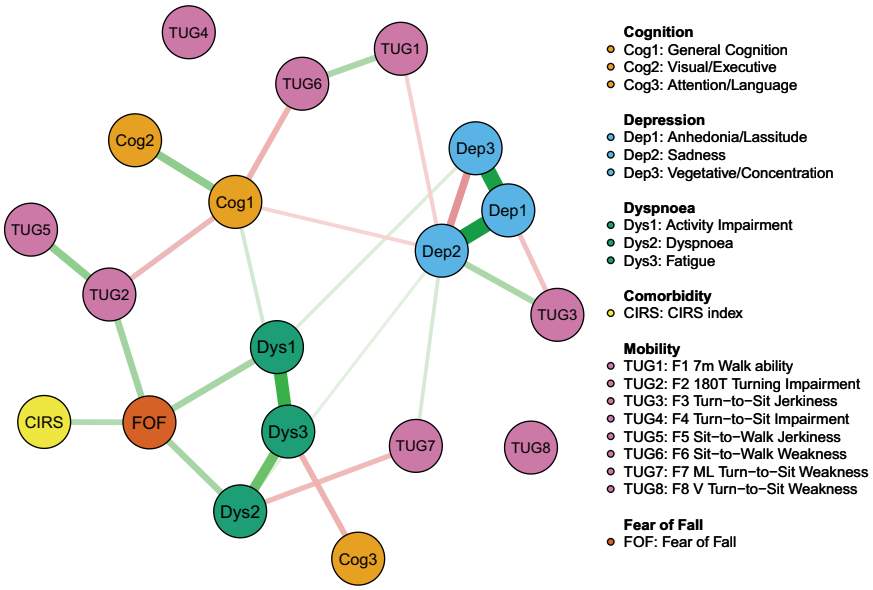

Figure 2. Network analysis of depression and somatic dimensions. The thickness of the line between two nodes is proportional of the strength of the association; green and red presents positive and negative correlations, respectively.

correlated with levels of dyspnea, fatigue, activity reduction, and fear of falling. Moreover, the *sadness* and *anhedonia/lassitude* complexes correlated with iTUG factor 1 (7 m Walking Ability). General cognitive abilities positively correlated with the *anhedonia/lassitude* complex, and negatively with factor 2 (180T Turning Impairment) and 6 (Sit-to-Walk weakness) from the iTUG; the executive function factor with fear of falling and factor 4 (Turn-to-Sit Impairment). The CIRS comorbidity index also correlated positively with levels of dyspnea, fatigue, activity reduction, and fear of falling.

We reexamined the associations between these factors using network analyses, highlighting the shared unique covariance between each couple of nodes after adjusting for all other variables (Figure 2; weighted adjacency matrix in Table 2). Connections were detected between the *sadness* depressive complex and 7 m Walking Ability (negative), Turn-to-Sit Jerkiness (positive), and Turn-to-Sit Weakness (positive), all in the direction of higher depressive severity linked with worse performance in the iTUG. S*adness* was also positively linked to dyspnea, which was in turn highly related to fatigue and fear of falling. The *anhedonia/lassitude* complex was negatively connected with factor 3 Turn-to-Sit Jerkiness (more fluid movement). The *neurovegetative/concentration* complex was positively connected with activity limitations, which was associated with fear of falling.

General cognitive abilities were connected with 180T Turning Impairment (negative), Sit-to-Walk weakness (negative), as well as executive functions (positive), *sadness* (negative), and fatigue (positive). Physical comorbidities were only connected with fear of falling, which represented a hub of the network, being associated with dyspnea, activity limitations, and 180T Turning Impairment.

Table 2. Weighted adjacency matrix of the network model.

	R^2	g_gen_cognition	f1_visuo_exec	f2_att_lang	n1_anhedonia _lassitude	n2_sadness	n3_veget _conc	activities	dyspnea	fatigue	CIRS _COMORB	F1.7 m Walking. Ability	F2.180T Turning. Impairment	F3.Turn-to-Sit. Jerkiness	F4.Turn-to-Sit. Impairment	F5.Sit.to. Walk. Jerkiness	F6.Sit.to. Walk. weakness	F7.ML. Turn.to.Sit. weakness	F8.V.Turn. to.Sit. weakness	fear_falls
g_gen_cognition	33%	.	.34	.	.	−.13	.	.	.	.13	.	.	−.22	.	.	.	−.23	.	.	.
f1_visuo_exec	15%	.34	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
f2_att_lang	22%	.	.	.	.	.	.	.	.	.23	.	.	.	.	.	.	.	.	.	.
n1_anhedonia_lassitude	92%	.	.	.	.	.77	.75	.	.	.	.	.	.	−.19	.	.	.	.	.	.
n2_sadness	83%	−.13	.	.	.77	.	−.33	.	.90	.	.	−.14	.	.26	.	.	.	.12	.	.
n3_veget_conc	80%	.	.	.	.75	−.33	.	.11	.	.	.	.	.	.	.	.	.	.	.	.
activities	**76%**	.	.	.	.	.	**.11**	.	.	**.60**	.	.	.	.	.	.	.	.	.	**.27**
dyspnea	68%	.	.	.	.	.90	.	.	.	.45	.	.	.	.	.	.	.	−.21	.	.27
fatigue	81%	.13	.	−.23	.	.	.	.60	.45	.	.	.	.	.	.	.	.	.	.	.
CIRS_COMORB	11%	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.23
F1 Walk ability	17%	.	.	.	.	−.14	.	.	.	.	.	.	.	.	.	.	.26	.	.	.
F2 turn impairment	31%	−.22	.	.	.	.	.	.	.	.	.	.	.	.	.	.34	.	.	.	.28
F3 Turn-Sit Jerkiness	9%	.	.	.	−.19	.26	.	.	.	.	.	.	.	.	.	.	.	.	.	.
F4 Final turn Impairment	0%	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
F5 Sit-to-Walk Jerkiness	14%	.	.	.	.	.	.	.	.	.	.	.	.34	.	.	.	.	.	.	.
F6 Sit-to-Walk weakness	14%	−.23	.	.	.	.	.	.	.	.	.	.26	.	.	.	.	.	.	.	.
F7 ML Turn-to-Sit weakness	13%	.	.	.	.	.12	.	.	−.21	.	.	.	.	.	.	.	.	.	.	.
F8 Turn-to-Sit weakness	0%	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
fear_falls	58%	.	.	.	.	.	.	.27	.27	.	.23	.	.28	.	.	.	.	.	.	.

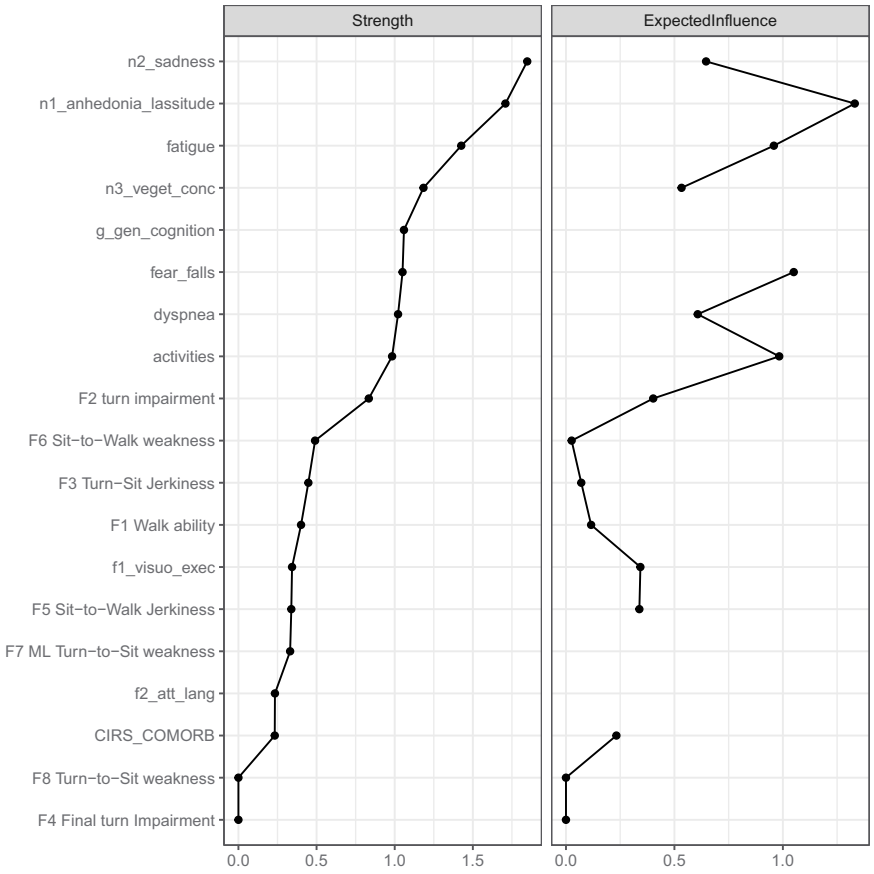

Figure 3. Centrality measures of strength and expected influence.

Node Centrality and Predictability

The nodes of *sadness* and *anhedonia/lassitude* presented the highest centrality in the network, followed by fatigue, general cognition, fear of fall, and dyspnea (Figure 3, left panel). Depressive symptoms also had high levels of expected influence with dyspnea, activity limitations, and fear of falling (Figure 3, right panel). Among factors from the iTUG, 180T Turning Impairment, Sit-to-Walk Jerkiness, and 7 m Walking Ability had the highest expected influence.

Discussion

We investigated how physical symptoms interact with residual depressive symptoms in older adults using an approach based on complexity, namely the network approach to psychopathology, and exploring the clinical domains of movement, fear of falling, and dyspnea. We found that the severity of depressive symptoms was associated with specific features of movement, namely worse turning ability, walking ability, and transitions from walking to sitting. Depressive symptoms were also associated with dyspnea, fear of falling, and cognitive abilities. Findings from this study can prompt research on the mechanism of

maintenance of residual depressive symptoms in older adults and identify clinical targets for integrated therapeutic approaches.

The *sadness* depression complex was connected with specific features of movement, namely Walking Ability, Turn-to-Sit Jerkiness, and Turn-to-Sit Weakness. These associations were independent of cognitive functions, physical comorbidities, and other potential confounders. These findings confirm that depression, mobility, and cognition are intrinsically interconnected, especially in old age (Belvederi Murri et al., 2020). Studies from the general population found that older individuals with depression present impairments of posture, balance, and gait. Depression is, in fact, associated with lower muscle strength, more frequently measured at the level of the hand grip but also in lower limbs (Bao et al., 2022; Zasadzka, Pieczyńska, Trzmiel, Kleka, & Pawlaczyk, 2021). Longitudinal studies suggest that in older adults impaired mobility precedes the onset of depression, different from younger individuals (Belvederi Murri et al., 2020). Thus, residual depressive symptoms may represent a reaction to the presence of movement-related disability. Consistently, we detected specific connections of sadness with activity limitations, fear of falling, and reduced turning ability that are known consequences of impaired movement (Cocks, Young, Ellmers, Jackson, & Williams, 2021). Among individuals with chronic major depression, this association might depend on various mechanisms at the neurobiological level, such as primary involvement of midbrain dopaminergic (Bennabi, Vandel, Papaxanthis, Pozzo, & Haffen, 2013; Felger & Treadway, 2017), cerebellar and vestibular systems. These may be particularly relevant for older adults with altered perception, motor planning, gravity-related balance, and motor decision-making (Hilber et al., 2019). Regardless of the underlying mechanisms, motor dysfunction should be investigated as a maintenance factor among individuals with depression who display residual symptoms (Janzing et al., 2020).

Network analyses suggested that dyspnea was another symptom linking the physical and psychological domain of depression: it was positively associated with the severity of sadness, as well as with fatigue and fear of falling. Dyspnea is the subjective experience of breathing discomfort, which depends on a discrepancy between interoceptive signals of the expected and accomplished respiratory flow (Fukushi, Pokorski, & Okada, 2021). It is strongly emotionally charged, and elicits anxiety even when physical illnesses are absent (Allen, Varga, & Heck, 2022; Harrison et al., 2021), often leading to physical exhaustion. Several studies suggest that dyspnea predicts the onset of depression and anxiety longitudinally (Neuman et al., 2006; Schuler, Wittmann, Faller, & Schultz, 2018; Trevisan et al., 2020; Yohannes et al., 2022), which is consistent with the role of this symptom in contributing to the maintenance of residual psychiatric symptomatology in major depression, even without a diagnosis of COPD.

The findings of this study may have direct clinical relevance. First, they suggest that walking ability, lack of coordination in movement, dyspnea, weakness, and fear of falling may contribute to maintaining residual depressive symptoms in older adults with major depression, even after treatment with antidepressant drugs. These clinical features may share a common link with impaired sensory somatosensory and interoceptive processes that are associated with depression (Eggart, Lange, Binser, Queri, & Müller-Oerlinghausen, 2019) but which may not be directly affected by antidepressant treatment (Burrows et al., 2022). Moreover, scarce data are available on the effects of psychotropic drugs on motor function in general (Beheydt et al., 2015) and even less on muscle strength (Nørregaard, Volkmann, & Danneskiold-Samstøe,

1995; Parise, Bosman, Boecker, Barry, & Tarnopolsky, 2001). Since motor abnormalities, dyspnea, and anxiety are common residual symptoms of late-life depression, our findings suggest they may be elective targets for specific therapeutic interventions, such as physical exercise, balance-motor rehabilitation, or proprioceptive rehabilitation (Abdelbasset et al., 2020; Belvederi Murri et al., 2018; Gambaro et al., 2022; Kendrick et al., 2014; Zou et al., 2019). The findings of this study also support the proposal to consider motor dysfunction among the clinical features of depression (Walther, Bernard, Mittal, & Shankman, 2019).

This study is strengthened by a reliable assessment of movement, as well as the inclusion of multiple somatic and cognitive dimensions that are known to interact with depressive symptoms. Moreover, the network approach allowed us to reliably explore multiple pathways of potential reciprocal interplay. However, the study limitations need to be acknowledged. First, the cross-sectional nature of the study prevents from drawing causal inferences on the direction of these associations. Second, the sample size was relatively small and comprised mostly men, which may limit the generalizability of findings. Also, findings may not generalize to patients who have not received antidepressant treatment. Nonetheless, patients are largely representative of those who are treated in primary care, both in terms of severity and concurrent clinical features. Third, we did not examine the role of specific physical illnesses in detail: recent studies suggest that different patterns of physical diseases might also hold specific relationship with depressive symptoms, and their role should be accounted for in future studies (Triolo et al., 2021). Fourth, given the exploratory nature of the study, findings should be interpreted with caution, especially considering the lack of more detailed measures of anxiety symptoms.

In conclusion, residual symptoms of late-life depression are associated with abnormal motor function, dyspnea, weakness, and fear of falling. These clinical dimensions may constitute elective therapeutic targets for novel rehabilitative interventions.

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We are grateful to the study participants for their engagement. The dataset of the current study is not available for the scientific community as (i) informed consent has not been provided for this purpose and (ii) additional analyses are currently being performed. Analyses carried out in this paper were not pre-specified. The analytic code file is available upon request.

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Dr. Belvederi Murri had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Belvederi Murri, Triolo, Chiari Zanetidou. Acquisition of the data: Nerozzi, Padula, Assirelli, Ermini, Bagnoli, Donato Zocchi, Tripi, Zanetidou. Data Analysis: Belvederi Murri, Coni. Interpretation of data: all authors. Drafting of the manuscript: Belvederi Murri, Triolo. Critical revision of the manuscript and approval of final draft: all authors.

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