Links Between Physical Frailty and Regional Gray Matter Volumes in Older Adults: A Voxel-Based Morphometry Study

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Physical frailty
regional gray matter volumes
voxel-based morphometry

Abstract

Objectives: The relationship between physical frailty and regional gray matter volume in the brain was investigated among community-dwelling older Japanese people.

Methods: Participants (N = 835; age range 65–89 years) were community-dwelling older adults in Obu City and Higashiura Town in Aichi Prefecture, Japan. Physical frailty was determined by the modified criteria of the Cardiovascular Health Study, which included weight loss, slowness, weakness, exhaustion, and low physical activity. Regional gray matter volumes were evaluated from 3-dimensional T1-weighted magnetic resonance images by statistical parametric mapping. The relationship between physical frailty and regional gray matter volume was analyzed with an analysis of covariance design using statistical parametric mapping adjusting for age, sex, and education level.

Results: The voxel-based analyses showed that physical frailty per se was not significantly associated with any brain region. However, weakness was associated with reduced gray matter volumes in the hippocampus, amygdala, and fusiform gyrus, and slowness was associated with reduced gray matter volumes in the hippocampus, amygdala, fusiform gyrus, medial prefrontal and orbitofrontal cortex, inferior frontal gyrus, primary somatosensory cortex, insula, superior temporal sulcus, and cerebellum. Other components of physical frailty were not associated with the gray matter volumes in any regions.

Conclusions and implications: The weakness and slowness components of physical frailty were linked to reduced gray matter volume in brain regions associated with not only physical mobility but also cognitive functions and social processes. This study addressed the underlying mechanisms in the progression of physical, cognitive, and social frailty, from the perspective of brain structures that are associated with frailty.

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Physical frailty is a crucial geriatric concept in aged societies, which is characterized by reduced physiological reserves and increased vulnerability to acute stress in older adults. Fried et al. used data from the Cardiovascular Health Study (CHS) and defined physical frailty through 5 components: weight loss, slowness, weakness, exhaustion, and low physical activity. A systematic review has indicated that physical frailty is prevalent in 10.7% (range 4.5%–59.1%) of community-dwelling older adults. Importantly, many studies have shown that physical frailty can effectively predict adverse outcomes such as falls, acute and chronic illnesses, disabilities, hospitalizations, and death.
Therefore, physical frailty is a useful predictor for estimating the functional prognosis and life expectancy of older adults, as well as a tool for providing comprehensive medical care. However, only a limited number of studies have examined the underlying neural basis of the progression of physical frailty.

We focused on structural neuroimaging analyses to explore brain regions that are associated with physical frailty among a community-dwelling older population. Only 1 pioneering study, known as the I-Lan Longitudinal Aging Study, conducted in Taiwan, has used voxel-based morphometric analysis to clarify the brain regions that are associated with physical frailty described by Fried et al. Chen et al showed a significant relationship between physical frailty and gray matter volumes in the cerebellum, hippocampus, and several other cerebral regions. However, the participants in the I-Lan study were young (50 years or older), and the proportion of participants who were physically frail was small (4.2%). In addition, basic and socio-demographic characteristics associated with physical frailty could be different among Taiwan, Japan, and other countries. Therefore, relationships between physical frailty and brain structures need to be addressed in different populations.

Another reason to address the association between physical frailty and brain regions is related to the concept of frailty itself, which includes not only physical but also cognitive and social aspects. It is essential to determine how physical, cognitive, and social elements of frailty progress by influencing each other. Notably, an international consensus group (IAGG) has defined cognitive frailty as an important clinical syndrome characterized by the simultaneous presence of both physical frailty and cognitive impairments in the absence of concurrent dementia. The accumulated data on the relationships between physical frailty and brain structures are essential for understanding the underlying mechanisms in the progression of physical, cognitive, and social frailty. In addition, limitations of research on physical frailty include the use of subjective assessments and different assessments of physical frailty, which suggest the importance of accumulating evidence on the relationship between the current framework of frailty and different objective outcomes.

In this study, we examined the relationships between physical frailty and regional gray matter volumes by analyzing structural magnetic resonance imaging (MRI) volumes collected from a sample of community-dwelling older Japanese people. We used voxel-based morphometry (VBM) to assess whether individual differences in brain structures were associated with physical frailty. Specifically, this study aimed (1) to examine whether physical frailty defined by the CHS criteria was associated with regional brain volumes and (2) to elucidate the components of physical frailty that are closely related to specific brain regions. It was expected that the results of this study would help address the underlying mechanisms in the progression of physical, cognitive, and social frailty from the perspective of brain structures that are associated with frailty.

Methods

Participants

The data in this study were collected as a part of the National Institute for Longevity Sciences—Longitudinal Study of Aging (NILS-LSA). The NILS-LSA is a Japanese, population-based, prospective cohort study of normal aging and age-related diseases. The participants were age- and sex-stratified random samples selected from Obu City and Higashiura Town in Aichi prefecture, Japan. The first-wave examination of the NILS-LSA was conducted from November 1997 to April 2000 and included 2267 participants (age range 40–79 years). These participants have been followed-up every 2 years and replaced by new, randomly recruited, age- and sex-matched participants when participants could not attend the follow-up investigations. The study protocol was approved by the Committee on the Ethics of Human Research. The written, informed consents of all the participants were obtained before their participation in the study. Details of the NILS-LSA have been reported elsewhere.

The participants of this study were people who completed the sixth wave of the study (n = 2302) because 3-dimensional MRI data (explained below) from the NILS-LSA were available at the sixth wave. The exclusion criteria for the study were (1) being 64 years or younger (n = 1331); (2) MR imaging not being conducted because of claustrophobia or other reasons (n = 49); (3) having defective MR imaging data (n = 3); (4) having a history of head surgery (n = 6); (5) having a history of dementia (n = 3); or (6) missing physical frailty data (details are explained below; n = 75). Based on these criteria, 835 older individuals (mean age: 74.26 years, SD = 5.88 years, age range = 65–89 years, women = 49.70%) participated in this study.

Assessment of Physical Frailty

We assessed physical frailty by using the 5 modified criteria described in the CHS: weight loss, slowness, weakness, exhaustion, and low physical activity. NLS-LSA conducts biennial examinations, and therefore, we defined weight loss as a 5% weight loss in the prior 2 years. Slowness was defined by a comfortable gait speed <1.0 m/s or disturbances of gait. Weakness was defined as a maximum grip strength <26 kg in men and <18 kg in women. Exhaustion was assessed by responses to self-reported questions that included 2 questions selected from the Center for Epidemiologic Studies Depression Scale: “I felt that everything I did was an effort” and “I could not get ‘going.’” Low physical activity was defined as the lowest 20% of leisure-time physical activity assessed by the modified Minnesota Leisure-time Physical Activity Questionnaire by sex. According to these definitions, we defined the physically frail group as having 3 or more limitations, the prefrail group as having 1 or 2 limitations, and the robust group as having no limitations.

Brain MRI Data Acquisition and Processing

All magnetic resonance imaging was performed with a 3.0-Tesla MRI-scanner (Siemens Magnetom Tim Trio, Erlangen, Germany) with the magnetization-prepared rapid gradient-echo imaging sequence. High-resolution 3-dimensional T1-weighted images were acquired (TR/TE/TI = 1.800/198/800 ms, 9-degree flip angle, 0.98 × 0.98 × 1.1 mm³ resolution, and 256 × 256 matrix). Image processing was conducted with statistical parametric mapping (SPM) 8 software (Wellcome Department of Imaging Neuroscience Group, London, UK; http://www.flimion.ucl.ac.uk/spm) running on MatLab. First, the MR images were segmented for gray and white matter using the segmentation tools in SPM 8. Subsequently, we performed diffeomorphic anatomical registration through exponentiated lie algebra for inter-subject registration of the gray matter (Supplementary Methods). Then, we applied voxel-based morphometry implemented in the VBM 8 toolbox (http://www.neuro.uni-jena.de/vbm) with default parameters. The details of diffeomorphic anatomical registration through exponentiated lie algebra-VBM have been described elsewhere.

Other Variables

Data on age, sex, education (years), marital status (married, unmarried), conditions of habitation (living alone, living with others), employment (employed, unemployed), current smoking status (smoker, nonsmoker), and chronic diseases (past and present hypertension, stroke, heart disease, diabetes mellitus, dyslipidemia, osteoporosis chronic bronchitis, and knee arthropathy) were collected by a self-administered questionnaire.
Statistical Analyses

Data were analyzed using the mean ± SD for continuous variables and the frequency (%) for categorical variables. Statistical differences in the above characteristics that were categorized by the group of physical frailty (frail, prefrail, or robust) were examined by using an analysis of variance and χ² tests.

An analysis of covariance design (SPM 8 software) with age, sex, and education entered as covariates were used to identify regional gray matter volumes related to physical frailty. Specifically, voxel wise gray matter volumes were analyzed between physical frailty (the frail group, the prefrail group, or the robust group) and each component (the presence or absence of weight loss, slowness, weakness, exhaustion, and low physical activity). The results were considered significant under the criteria of familywise error corrected P value of <.05 at height (P = .001).

Results

Participant Characteristics

Of the 835 participants, 78 participants were in the frail group (9.3%), 428 were in the prefrail group (51.3%), and 329 were in the robust group (39.4%). The prevalence of each determinant component of the frailty phenotype, including weight loss, slowness, weakness, exhaustion, and low physical activity, was 17.5%, 10.2%, 15.3%, 37.5%, and 20.8%, respectively.

Table 1 shows participant characteristics according to their physical frailty status. Physical frailty was significantly associated with age, sex, education, marital status, conditions of habitation, employment, heart disease, osteoporosis, and knee arthropathy. However, additional age-adjusted analyses indicated that only sex and education were significantly associated with physical frailty. Therefore, the following analyses were adjusted for age, sex, and education.

Table 1 Participant Characteristics by Physical Frailty Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 835)</th>
<th>Frail (n = 78)</th>
<th>Prefrail (n = 428)</th>
<th>Robust (n = 329)</th>
<th>χ²/F Value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>74.3 ± 5.9</td>
<td>79.2 ± 6.3</td>
<td>74.6 ± 5.8</td>
<td>72.7 ± 5.1</td>
<td>F = 43.00</td>
<td>.001</td>
</tr>
<tr>
<td>Sex, women, n (%)</td>
<td>415 (49.7)</td>
<td>54 (69.2)</td>
<td>224 (52.3)</td>
<td>137 (41.6)</td>
<td>χ² = 21.6</td>
<td>.001</td>
</tr>
<tr>
<td>Education year</td>
<td>11.3 ± 2.6</td>
<td>10.5 ± 2.7</td>
<td>11.1 ± 2.5</td>
<td>11.8 ± 2.8</td>
<td>F = 11.50</td>
<td>.001</td>
</tr>
<tr>
<td>Marital status, married, n (%)</td>
<td>646 (77.4)</td>
<td>49 (62.8)</td>
<td>311 (72.7)</td>
<td>286 (86.9)</td>
<td>χ² = 32.0</td>
<td>.001</td>
</tr>
<tr>
<td>Conditions of habitation, living alone, n (%)</td>
<td>59 (11.9)</td>
<td>13 (16.7)</td>
<td>60 (14.0)</td>
<td>26 (7.9)</td>
<td>χ² = 8.56</td>
<td>.014</td>
</tr>
<tr>
<td>Employment, having an occupation, n (%)</td>
<td>194 (23.2)</td>
<td>13 (16.7)</td>
<td>90 (21.0)</td>
<td>91 (27.7)</td>
<td>χ² = 6.67</td>
<td>.036</td>
</tr>
<tr>
<td>Current smoking, smoker, n (%)</td>
<td>74 (8.7)</td>
<td>8 (10.3)</td>
<td>43 (10.1)</td>
<td>23 (7.0)</td>
<td>χ² = 2.36</td>
<td>.308</td>
</tr>
<tr>
<td>Hypertension, present, n (%)</td>
<td>397 (47.5)</td>
<td>44 (56.4)</td>
<td>206 (48.1)</td>
<td>147 (44.7)</td>
<td>χ² = 3.60</td>
<td>.165</td>
</tr>
<tr>
<td>Stroke, present, n (%)</td>
<td>65 (7.8)</td>
<td>11 (14.1)</td>
<td>32 (7.48)</td>
<td>22 (6.7)</td>
<td>χ² = 4.95</td>
<td>.084</td>
</tr>
<tr>
<td>Heart disease, present, n (%)</td>
<td>61 (7.3)</td>
<td>11 (14.1)</td>
<td>33 (7.71)</td>
<td>17 (5.2)</td>
<td>χ² = 7.65</td>
<td>.022</td>
</tr>
<tr>
<td>Diabetes, present, n (%)</td>
<td>95 (11.4)</td>
<td>10 (12.8)</td>
<td>52 (12.2)</td>
<td>33 (10.0)</td>
<td>χ² = 1.01</td>
<td>.605</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>210 (25.2)</td>
<td>22 (28.2)</td>
<td>103 (24.1)</td>
<td>85 (25.8)</td>
<td>χ² = 0.23</td>
<td>.692</td>
</tr>
<tr>
<td>Osteoporosis, n (%)</td>
<td>107 (12.8)</td>
<td>21 (26.9)</td>
<td>56 (13.1)</td>
<td>30 (9.1)</td>
<td>χ² = 17.95</td>
<td>.001</td>
</tr>
<tr>
<td>Chronic bronchitis, n (%)</td>
<td>28 (3.4)</td>
<td>4 (5.1)</td>
<td>13 (3.0)</td>
<td>11 (3.3)</td>
<td>χ² = 0.89</td>
<td>.641</td>
</tr>
<tr>
<td>Knee arthropathy, n (%)</td>
<td>134 (16.1)</td>
<td>21 (26.9)</td>
<td>74 (17.3)</td>
<td>39 (11.9)</td>
<td>χ² = 11.63</td>
<td>.003</td>
</tr>
<tr>
<td>Frailty component</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Weight loss, present, n (%)</td>
<td>146 (17.5)</td>
<td>50 (64.1)</td>
<td>96 (22.4)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slowness, present, n (%)</td>
<td>85 (10.2)</td>
<td>45 (57.7)</td>
<td>40 (9.90)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness, present, n (%)</td>
<td>128 (15.3)</td>
<td>59 (75.6)</td>
<td>69 (16.1)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhaustion, present, n (%)</td>
<td>313 (37.5)</td>
<td>63 (80.8)</td>
<td>250 (58.4)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low physical activity, present, n (%)</td>
<td>174 (20.8)</td>
<td>43 (55.1)</td>
<td>131 (30.6)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legal and Ethical Approval

The present study was approved by the Institutional Review Board of the University of Tokyo. All participants provided written informed consent before participation. The present study adhered to the Declaration of Helsinki.

Longitudinal Aging Study

We conducted a longitudinal study to investigate the relationships between physical frailty and regional gray matter volumes (the I-Lan Longitudinal Aging Study). However, we did not find a significant difference between the 2 groups.

Components of Physical Frailty and Regional Gray Matter Volumes

We then examined whether the 5 components of physical frailty were associated with regional gray matter volume using VBM analysis. The results indicated that weakness determined by grip strength and slowness determined by gait speed were significantly and negatively associated with the gray matter volumes of specific regions.

Figure 1 shows the regions in which gray matter volume was associated with weakness. It can be seen from the figure that weakness was significantly associated with reduced gray matter volumes in the right anterior hippocampal and amygdala clusters (Figure 1A and B) and the bilateral fusiform gyrus (Figure 1A and C).

Figure 2 shows the regions in which gray matter volume was associated with slowness. Regions significantly associated with slowness overlapped with regions significantly associated with weakness: the bilateral hippocampus and amygdala (Figure 2A and B) and fusiform gyrus (Figure 2A and C).

On the other hand, weight loss, exhaustion, or low physical activity was not associated with gray matter volumes in any regions.

Discussion

We investigated the relationships between physical frailty and regional gray matter volumes. The results indicated that physical frailty defined by the CHS criteria was not associated with any brain region. However, weakness and slowness were significantly related to gray matter volumes in specific regions (Figures 1 and 2). We also conducted additional analyses after adjusting for all the characteristic variables (Table 1), which produced the nearly identical result (Supplementary Figures 3 and 4).

Weakness and slowness have been consistently associated with hippocampus, amygdala, and fusiform gyrus (Figures 1 and 2; Supplementary Figures 1 and 2). Hippocampus is a structure that is crucial for cognitive function, especially episodic memory and spatial navigation.16,17 Hippocampal atrophy occurs during the progression of Alzheimer’s disease and several types of non-Alzheimer's dementia.
For healthy older people, decreased hippocampal volume and amygdala volume precede the first signs of cognitive decline. Our additional analyses showed that weakness and slowness had significant associations with the Mini-Mental State Examination score, which is indicative of cognitive functions (Supplementary Table 1). These results suggest that weakness and slowness, hippocampal and amygdala volumes, and cognitive functions might be closely linked to each other.

Interestingly, weakness and slowness were also related to reduced volumes of brain regions associated with social processes. For example, the volume of the amygdala is correlated with the size and complexity of social networks. Amygdala and anterior hippocampus are associated with emotional experience and regulation, which determine adaptive responses to social interactions. Fusiform gyrus, also called the fusiform face area, is a part of the visual system that is specialized for face perception and facilitates social interactions. Our additional analyses indicated that weakness and slowness were negatively correlated with the Center for Epidemiologic Studies Depression Scale score that assesses depressed mood, which includes interpersonal affect (Supplementary Table 1).

Slowness was associated with more extensive reductions in other brain region volumes. The relationships between slowness and reduced cerebellar volume is predictable because the cerebellum is known to play a critical role in physical mobility. In addition, slowness was associated with several brain regions related to social processes concerned with understanding others and adapting to social relationships. Medial prefrontal cortex is known as an area for human social cognition and behavior. Orbitofrontal cortex involves more general processing of emotions recognition of emotions in others. Inferior frontal gyrus is associated with voice perception, including emphasis and emotional tones. Primary somatosensory cortex plays a crucial role in the comprehensive representation of body state associated with emotional or social behavior. Insula is associated with the affect sharing processes. Moreover, superior temporal sulcus is implicated in various social processes, ranging from language...
perception to simulating the mental processes of others.\textsuperscript{25,27} The additional analyses indicated that total gray and white matter volumes were significantly associated with slowness (Supplementary Table 2), which suggest that slowness might be related to the atrophy of the whole brain, including the above-discussed brain regions.

It has been reported that weakness and slowness, which were shown to be related to brain structure in this study, are the first emerging components of physical frailty.\textsuperscript{28} They might present as mobility-type frailty, which are the core determinants of physical frailty and sarcopenia as well as significant predictors of adverse clinical outcomes.\textsuperscript{7,29–31} Recent research has recommended using weakness and slowness as diagnostic criteria of cognitive frailty.\textsuperscript{32,33} The current results also suggest the importance of weakness and slowness in relation to changes in brain structures. We conducted a supplementary VBM analysis to examine whether the combination of weakness and slowness correlated with more severe brain atrophy. The results of this analysis indicated that the association of weakness and slowness with the brain volume was more significant when both weakness and slowness was observed than either weakness or slowness (Supplementary Figure 5). Therefore, mobility-type frailty\textsuperscript{29} might be most closely associated with regional brain volumes.

In summary, weakness and slowness, which are the components of mobility-type frailty, were associated with a reduction of gray matter volume in brain regions known to be related not only to physical mobility but also to cognitive functions and social processes. The results of the current study suggest that physical, cognitive, and social components of frailty might closely interact with each other because of their related neural pathology. We suggest a following hypothesis based on the findings of this study: physical frailty increases in old age because of the reduction in the size of brain structures, and physical frailty leads to decreased cognitive and social stimulation, which in turn leads to the atrophy of brain regions related to cognitive and social functions, which results in a vicious cycle. Future longitudinal studies are required to clarify the causal relationships and confirm the above hypothesis.

Specific results of this study were partially inconsistent with the pioneering I-LAN Study.\textsuperscript{7} We found an association between components of physical frailty and reductions in the volume of specific brain

Fig. 2. Regions where gray matter volume was significantly and negatively associated with slowness (familywise error corrected cluster \( P < .05 \), at height \( P = .001 \)). (A) Statistically significant clusters are shown on the 3-dimensional brain surface. (B) and (C) Statistically significant clusters are shown on the 2 representative sagittal, coronal, and axial slices at the intersection of the blue lines. The color bar illustrates the corresponding t values. The t values indicate the test statistic calculated based on the voxel, and larger values indicate stronger associations between slowness and regional brain volumes. For reference, we identified 3 brain regions that are commonly correlated with weakness and slowness and developed scatter plots using MarsBaR toolbox (http://marsbar.sourceforge.net/), which are displayed in Supplementary Figure 2.
regions related to social processes, which was not reported in the study by Chen et al. One reason for this inconsistency could be differences in the basic characteristics of participants, such as their age and educational level. For example, it is possible that associations between physical, cognitive, and social aspects of frailty increase in older adults. As a result, this relationship needs to be investigated in other populations.

This study has several limitations. First, the cross-sectional design of the study does not allow us to make conclusions about the causal relationships between physical frailty and brain structures. Further longitudinal studies are needed to clarify the detailed mechanisms of any causal relationships. Second, our study did not assess cognitive or social frailty. Therefore, the association of brain structures with cognitive and social frailty, and the progression of cognitive and social frailty remain unclear. This association might be clarified by investigating how the combination of physical frailty, cognitive decline, and decreased social relationships is associated with brain structures. Third, physical frailty and brain structures might be associated with other factors that this study did not investigate. For example, it has been suggested that slow gait, which is an index of slowness, is associated with fear of falling, weak eyesight, and reduced muscle mass, among others. We suggest that future studies should also consider these variables when investigating relationships between components of physical frailty and brain structures. Finally, unlike functional MRI, it is impossible for structural MRI to investigate changes in brain activation patterns over time or verify functional interactions between distant brain regions. However, an essential advantage of structural MRI studies is that they enable associating measurements of brain structures obtained by MRI scans with individual differences measured in ecologically valid environments outside the scanner. Therefore, it would be possible for future longitudinal studies to identify network structures of the brain by examining structural covariation of brain regions.

Despite the above limitations, however, the current study is a pioneering investigation of the neural pathophysiology underlying the progression of physical frailty that has provided essential data for understanding the progression of frailty.

Conclusions and Implications

The weakness and slowness components of physical frailty were linked with reduced gray matter volume in brain regions associated with not only physical mobility but also cognitive functions and social processes. This study addressed the underlying mechanisms in the progression of physical, cognitive, and social frailty from the perspective of brain structures that are associated with frailty.

Acknowledgments

We are extremely grateful to all the study participants for completing the surveys for this study. We are also thankful to our colleagues in the Section of NILS-LSA and the Department of Clinical and Experimental Neuroimaging for their support in conducting this study.

References

Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra

Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL)\(^1\) is an algorithm for diffeomorphic image registration, which has been formulated to include an option for estimating inverse consistent deformations. Nonlinear registration is considered to be a local optimization problem, which is solved by using a Levenberg–Marquardt strategy. The necessary matrix solutions are obtained using a multigrid method. A constant Eulerian velocity framework is used, which allows a rapid scaling and squaring method to be used in the computations.

Reference

Supplementary Figure 1. Scatter plots showing relationships between volumes of 3 brain regions and weakness. We identified the brain regions that were commonly correlated with weakness and slowness (A: right anterior hippocampus/amygdala, B: left fusiform, C: right fusiform) from threshold statistical maps of the results of regression analyses and developed scatter plots using MarsBaR toolbox for SPM (http://marsbar.sourceforge.net).
Supplementary Figure 2. Scatter plots showing the relationships between volumes of 3 brain regions and slowness. We identified the brain regions that were commonly correlated with weakness and slowness (A: right anterior hippocampus/amygdala, B: left fusiform, C: right fusiform) from threshold statistical maps of the results of regression analyses and developed scatter plots using MarsBaR toolbox for SPM (http://marsbar.sourceforge.net).
Supplementary Figure 3. Regions where gray matter volume was significantly and negatively associated with weakness (familywise error corrected cluster P < .05, at height P = .001). (A) The results of analyses after adjusting for age, sex, and years of education. (B) The results of analyses after adjusting for all the covariates (age, sex, education, marital status, conditions of habitation, employment, current smoking status, and chronic diseases). The color bar illustrates the corresponding t value.
Supplementary Figure 4. Regions where gray matter volume was significantly and negatively associated with slowness (familywise error corrected cluster \( P < .05 \), at height \( P = .001 \)). (A) The results of analyses after adjusting for age, sex, and years of education. (B) The results of analyses after adjusting for all the covariates (age, sex, education, marital status, conditions of habitation, employment, current smoking status, and chronic diseases). The color bar illustrates the corresponding t value.
Supplementary Figure 5. Result of a regression analysis examining the correlation between combined weakness and slowness with brain atrophy after establishing 3 groups; a group that corresponds to neither weakness nor slowness (coding = 0), a group that corresponds to either weakness or slowness (coding = 1), and a group that corresponds to both weakness and slowness (coding = 2). Age, sex, and education were adjusted. (A) Statistically significant clusters are shown on the 3-dimensional brain surface. (B), (C) Statistically significant clusters are shown on the 2 representative sagittal, coronal, and axial slices at the intersection of blue lines. The color bar illustrates the corresponding t value.
## Supplementary Table 1
The Association of MMSE and CES-D Scores With Components of Physical Frailty

<table>
<thead>
<tr>
<th></th>
<th>MMSE Scores</th>
<th>CES-D Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>GLM*</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfrail</td>
<td>27.5 ± 0.08</td>
<td>F = 0.55</td>
</tr>
<tr>
<td>Frail</td>
<td>27.6 ± 0.18</td>
<td></td>
</tr>
<tr>
<td>Slowness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfrail</td>
<td>27.6 ± 0.08</td>
<td>F = 8.44</td>
</tr>
<tr>
<td>Frail</td>
<td>26.8 ± 0.24</td>
<td></td>
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<tr>
<td>Weakness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfrail</td>
<td>27.6 ± 0.08</td>
<td>F = 12.78</td>
</tr>
<tr>
<td>Frail</td>
<td>26.9 ± 0.19</td>
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<tr>
<td>Exhaustion</td>
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</tr>
<tr>
<td>Nonfrail</td>
<td>27.6 ± 0.09</td>
<td>F = 0.79</td>
</tr>
<tr>
<td>Frail</td>
<td>27.4 ± 0.12</td>
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<tr>
<td>Low physical activity</td>
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</tr>
<tr>
<td>Nonfrail</td>
<td>27.5 ± 0.08</td>
<td>F = 0.13</td>
</tr>
<tr>
<td>Frail</td>
<td>27.5 ± 0.16</td>
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</tr>
</tbody>
</table>

CES-D, Center for Epidemiologic Studies Depression Scale (possible score is 0-60); GLM, general linear model; MMSE, Mini-Mental State Examination (possible score is 0-30).
*Adjusted for age, sex, education.

## Supplementary Table 2
The Association of Total Gray Matter Volume and Total White Matter Volume With Components of Physical Frailty

<table>
<thead>
<tr>
<th></th>
<th>Total Gray Matter Volume (mm³)</th>
<th>Total White Matter Volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>GLM*</td>
</tr>
<tr>
<td>Weight loss</td>
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<td></td>
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<tr>
<td>Nonfrail</td>
<td>517,646.73 ± 1212.05</td>
<td>F = 1.58</td>
</tr>
<tr>
<td>Frail</td>
<td>513,961.56 ± 2656.84</td>
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</tr>
<tr>
<td>Slowness</td>
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<tr>
<td>Nonfrail</td>
<td>518,398.76 ± 1156.54</td>
<td>F = 13.19</td>
</tr>
<tr>
<td>Frail</td>
<td>504,370.24 ± 3645.65</td>
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<tr>
<td>Weakness</td>
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<td>Nonfrail</td>
<td>517,791.98 ± 1203.58</td>
<td>F = 2.56</td>
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<tr>
<td>Frail</td>
<td>512,589.19 ± 2969.31</td>
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<td>Nonfrail</td>
<td>516,256.38 ± 1397.32</td>
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<td>Frail</td>
<td>518,246.61 ± 1810.07</td>
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<td>Low physical activity</td>
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<td>Nonfrail</td>
<td>517,772.45 ± 1236.92</td>
<td>F = 1.83</td>
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<tr>
<td>Frail</td>
<td>514,084.91 ± 2420.27</td>
<td></td>
</tr>
</tbody>
</table>

GLM, general linear model.
Total gray matter volume and total white matter volume were calculated using FreeSurfer (v 5.3).
*Adjusted for age, sex, education.