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Abstract

Background. Concern about falling is common in older people. Various related psychological constructs as well as poor balance and slow gait have been associated with decreased gray matter (GM) volume in old age. The current study investigates the association between concern about falling and voxel-wise GM volumes. Methods. A total of 281 community-dwelling older people aged 70–90 years underwent structural magnetic resonance imaging. Concern about falling was assessed using Falls Efficacy Scale-International (FES-I). For each participant, voxel-wise GM volumes were generated with voxel-based morphometry and regressed on raw FES-I scores (p < .05 family-wise error corrected on cluster level). Results. FES-I scores were negatively correlated with total brain volume (r = −.212; p ≤ .001), GM volume (r = −.210; p ≤ .001), and white matter volume (r = −.155; p ≤ .001). Voxel-based morphometry analysis revealed significant negative associations between FES-I and GM volumes of (i) left cerebellum and bilateral inferior occipital gyrus (voxels-in-cluster = 2,981; p < .001) and (ii) bilateral superior frontal gyrus [...]

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Regional Gray Matter Volumes Are Related to Concern About Falling in Older People: A Voxel-Based Morphometric Study

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Abstract

Background. Concern about falling is common in older people. Various related psychological constructs as well as poor balance and slow gait have been associated with decreased gray matter (GM) volume in old age. The current study investigates the association between concern about falling and voxel-wise GM volumes.

Methods. A total of 281 community-dwelling older people aged 70–90 years underwent structural magnetic resonance imaging. Concern about falling was assessed using Falls Efficacy Scale-International (FES-I). For each participant, voxel-wise GM volumes were generated with voxel-based morphometry and regressed on raw FES-I scores ($p < .05$ family-wise error corrected on cluster level).

Results. FES-I scores were negatively correlated with total brain volume ($r = -.212; p \leq .001$), GM volume ($r = -.210; p \leq .001$), and white matter volume ($r = -.155; p \leq .001$). Voxel-based morphometry analysis revealed significant negative associations between FES-I and GM volumes of (i) left cerebellum and bilateral inferior occipital gyrus (voxels-in-cluster = 2,981; $p < .001$) and (ii) bilateral superior frontal gyrus and left supplementary motor area (voxels-in-cluster = 1,900; $p = .004$). Additional adjustment for vision and physical fall risk did not alter these associations. After adjustment for anxiety, only left cerebellum and bilateral inferior occipital gyrus remained negatively associated with FES-I scores (voxels-in-cluster = 2,426; $p < .001$). Adjustment for neuroticism removed all associations between FES-I and GM volumes.

Conclusions. Our study findings show that concern about falling is negatively associated with brain volumes in areas important for emotional control and for motor control, executive functions and visual processing in a large sample of older men and women. Regression analyses suggest that these relationships were primarily accounted for by psychological factors (generalized anxiety and neuroticism) and not by physical fall risk or vision.

Key Words: Accidental falls—Fear of falling—Aged—Magnetic resonance imaging—Brain atrophy—Personality—Neurodegeneration—Psychological distress.

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Concern about falling is common in old age and reported by half of community-dwelling older people (1). Previous studies have shown that concern about falling is associated with measures of balance, gait and falls (2–4) as well as reduced quality of life and independence resulting from unnecessary restriction in daily activities (5). Concern about falling has also been associated with generalized anxiety, depressed mood and neurotic personality traits irrespective of previous falls or poor balance (4,6,7).

Generalized brain atrophy and reductions in gray matter (GM) volume have been consistently reported in old age. The prefrontal cortex is particularly susceptible to age-related GM atrophy, compared with the relative sparing of the more posterior regions of the brain (8). The prefrontal areas together with the motor cortex and cerebellum are important for balance and gait because of their involvement in the planning, control, and execution of voluntary movements (9,10). Differential age effects in these cortical areas may therefore contribute to decreased performance during motor tasks, especially those requiring more attention (ie, when dual tasking), and increase the risk of falling (9,10). Furthermore, it has been suggested that depressed mood, generalized anxiety, neurotic personality traits, and stress can accelerate this age-related neurodegeneration (11). The amygdala and hippocampal areas are particularly prone to neuronal cell loss as a result of long-term exposure to psychological stress (11). The hippocampus and amygdala, together with the cerebellum and prefrontal cortex, are important in recognizing and interpreting the significance of negative events (eg, falls). Because of their involvement in higher level behavior and emotional control (11,12), these cortical areas could contribute to a person’s level of concern about falling.

Recently, Davis and coworkers reported associations between lower fall-related self-efficacy (similar to high concern about falls) and smaller total brain volume and total GM volume (13). However, the underlying mechanisms for this association remain unclear. While the majority of older people with higher levels of concern about falling make an accurate reflection of their impaired balance, it has been suggested that about one in five rate their fall risk as high despite having good balance (4). People with such inappropriately high levels of concern also report higher levels of neuroticism (4). Therefore, on the one hand, it is possible that the association between concern about falling and reduced GM may be mediated by an actual (instability-related) fall risk (13). On the other hand, any observed association between concern about falling and a decline in GM volume could also be explained through lifestyle and/or biological pathways related to neurotic personality traits (11,14). The current study aimed to enhance our understanding of the association between fall-related psychological factors (high concern about falling) and lower GM volumes in a sample of 281 community-dwelling older men and women. Firstly, voxel-based morphometry (VBM) was applied to investigate focal differences in brain anatomy in combination with comparisons of volumes in different regions of interest across participants in an unbiased manner. Secondly, we explored the relative contribution of the identified GM regions and physical fall risk, neuroticism and generalized anxiety to elucidate the underlying mechanisms of this association. The overall hypothesized conceptual model is presented in Figure 1.

Methods

Participants
Participants for this study were drawn from a cohort of 1,037 cognitively intact, community-dwelling men and women (70–90 years) taking part in the first stage of the Sydney Memory and Ageing Study (MAS, January 2006 to October 2007). These participants were recruited randomly through the electoral roll in Eastern Sydney, with enrolment being compulsory for Australian citizens. The first 500 participants also agreed to participate in a prospective cohort study with a 1-year follow-up for falls. Of the total (1,037) participants, magnetic resonance imaging (MRI) scans were performed on 554 individuals. For the current study, included participants were those who consented to take part in the fall risk study and were eligible and consented to an MRI. The detailed methodology of MAS has been published previously (15). Exclusion criteria were previous diagnosis of dementia or developmental disability, psychotic symptoms, Parkinson’s disease, multiple sclerosis, motor neuron disease or central nervous system inflammation, progressive malignancy, Mini-Mental State Examination (MMSE) score of less than 24, or medical or psychological conditions that might hinder participants from completing assessments. For this substudy, further exclusion criteria were an inability to walk 20 m without a walking aid due to a neurological, cardiovascular or major musculoskeletal impairment, and contraindication to an MRI scan, such as a pacemaker or other metallic implants. The study was approved by the University of
NSW Human Studies Ethics Committee and informed consent was obtained from all participants.

**Measures**

Participants underwent a comprehensive assessment at baseline including neuropsychological, medical, and physiological measures.

**Neuropsychological assessment**

The Falls Efficacy Scale-International (FES-I) was used to assess participants’ levels about concern about falling across a wide range of activities of daily living (such as cleaning the house, shopping, walking on uneven surfaces). The FES-I is a self-report questionnaire containing 16 items where each item is rated on a 4-point scale (1 = not at all concerned to 4 = very concerned) (16). Symptoms of anxiety in the past month were assessed with the nine-item Goldberg Anxiety Scale (GAS) (17). Scores range between 0 and 9 for the number of symptoms of anxiety (18). Neurotic personality traits were assessed with one subdomain of the NEO five-factor inventory (19). We assessed global cognition using the MMSE, which is a widely used and well-known questionnaire used to detect cognitive impairment (ie, MMSE < 24). It is scored on a 30-point scale with a median score of 28 for healthy community-dwelling over 80 with more than 12 years of education (18).

**Medical assessment**

Medical conditions, medication use, and falls history were assessed in a face-to-face interview in order to gain a complete medical history of each participant. As a measure of comorbidity, each medical condition was given one point from a list of nine system-related conditions (ie, cardiovascular, respiratory, musculoskeletal, endocrine, urogenital, cancer, neurological, mental health, and eye diseases). A cardiovascular risk (CVR) factor index was assessed and implemented based on the D’Agostino and coworkers regression model (20) using following baseline data: age, current smoking status, diabetic status, systolic blood pressure, total cholesterol level, high-density lipoprotein level, and currently taking antihypertensive medication. General disability was assessed across six domains (understanding/communicating, mobility, self-care, interpersonal interactions, household/work activities, and participation in society) using the 12-item World Health Organization Disability Assessment Schedule (WHODAS II; total score range 0–36) (21).

**Physiological assessment**

In order to obtain an estimate of fall risk, we used the Physiological Profile Assessment (PPA; Neuroscience Research Australia, Sydney, New South Wales, Australia) (22). The PPA contains five validated measures of physiological function: visual contrast sensitivity, assessed with Melbourne edge test (MET); proprioception, measured with a lower limb-matching task, where errors in degrees are recorded with a protractor inscribed on a vertical clear acrylic sheet placed between the legs; quadriceps strength, measured isometrically in the dominant leg while participants are seated with hip and knee flexed to 90°; simple reaction time, measured with light as stimulus and finger press as response; and postural sway, measured with a sway meter recording displacements of the body at the level of the pelvis while participants stand on a foam rubber mat with eyes open.

**MRI acquisition**

Of the 281 participants, 237 were scanned using a Philips 3T Intera Quasar scanner (Philips Medical Systems, Best, The Netherlands) located at Neuroscience Research Australia, Sydney. Acquisition parameters have been reported previously in the Sydney MAS protocols. The remaining 44 subjects were scanned on a Philips 3T Achieva Quasar Dual scanner which replaced the original one in 2007 due to reasons outside of the investigators’ control. Acquisition parameters for all T1-weighted structural MRI scans were: repetition time = 6.39 ms, time to echo = 2.9 ms, flip angle = 8°, matrix size = 256 × 256, field of view = 256 × 256 × 190, and slice thickness = 1 mm with no gap between; yielding 1 × 1 × 1 mm³ isotropic voxels. A binary “scanner” variable was included in the statistical analysis as a covariate to minimize the scanner effect on GM volume. Intracranial volume (ICV) was calculated as the sum of total GM, white matter (WM), and cerebrospinal fluid volumes, and the ratio of the GM and WM volume to ICV was calculated to give the brain atrophy ratio. White matter hyperintensities (WMH) were identified on fluid-attenuated inversion recovery sequences and co-registered with a T1-weighted structural image. A validated automatic procedure was carried out to calculate WMH volume. The detailed methodology has been published previously (23).

**Image processing**

We applied the approach of VBM in image processing by running Statistical Parametric Mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London, UK). Initially, all T1-weighted MRI scans were visually inspected for abnormalities. Next, using the Hidden Markov Random Field option, unified segmentation in SPM5 was performed to segment T1 images into different tissues with the most commonly used ICBM152 atlas as the template. Subsequently, Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolbox was used to generate a series of customized templates and flow fields of GM and WM from all included images by performing iterative registration. Each individual image was then registered to the group templates to create the modulated warped tissue class image. Spatial normalization of GM to the Montreal Neurological Institute (MNI) space was achieved by using an affine transformation to the ICBM152 template. A 12-mm full-width half-maximum Gaussian kernel smoothing was then performed to generate the voxel-based GM volumes for each participant for the subsequent statistical analysis. A 12-mm full-width half-maximum Gaussian kernel was chosen as it is widely used in processing T1-weighted structural image, especially in samples including older adults as there may be more individual variations on GM volumes.

**Statistical analysis**

Neuropathological correlates of concern about falling (FES-I), generalized anxiety (GAS), neuroticism (NEO-FFI), and physical fall risk (PPA) were examined using the SPM5 package, in which the GM volume for each voxel was regressed on the raw score of each scale. Age, gender, ICV, and CVR were included in all statistical analyses as covariates of no interest, to adjust for global differences within our population (24). Anxiety, neuroticism, and physical fall risk were selected a priori as potential mediators, because of their established association with FES-I (4) and GM volume (9,11). Vision was added as a potential mediator based on the results of the initial analyses showing a strong correlation between FES-I and reduced GM volume in the occipital lobe. Therefore, to rule out the influence of clinical pathology on the relationship between voxel-wise GM volume and FES-I, we performed four additional correlation analyses, which were all controlled for age, gender, ICV, scanner, and CVR. The four analyses were different in that they included one additional
covariate, with adjustment for either (i) physiological fall risk (PPA), (ii) vision (MET), (iii) generalized anxiety (GAS), or (iv) neuroticism. All analyses were corrected for multiple dependent comparisons across the entire brain using the Theory of Gaussian Random Fields and based on the local maxima of the \( t \) statistic (24). The significance level for all correlation analyses was set at voxel-level significance of \( p \) less than .01 (uncorrected) combined with cluster-level significance of \( p \) less than .05 (family-wise error corrected). Anatomical locations of peak voxels were determined using anatomical labeling provided with xjView 8 software. Coordinates for peak voxels in suprathreshold clusters were provided, with \( x \), \( y \), and \( z \) values indicating voxel distance from the anterior fissure in sagittal, coronal, and axial planes in millimeters in the standard MNI space. Additionally, we used SPSS version 20 to report on descriptive data for all variables of interest. For data that were normally distributed, we report mean and SD. We used the Spearman \( \rho \) correlation coefficient to determine the level of association between brain volume ratios and age, gender, years of education, FES-I, WHODAS, GAS, neuroticism, MMSE, PPA, and CVR (Figure 2).

Results

Demographic, health, neuropsychological and physical characteristics are reported in Table 1. Mean age of participants was 77.8 years (SD 4.5) and 151 (53.3\%) were women. The cohort had an average of 11.5 (SD 3.5) years of education and 206 (73\%) participants rated their health as good or very good. Levels of concern about falling, neurotic personality traits, and anxiety were reflective of a representative sample of community-dwelling older adults (15). The cohort had a mean total brain volume (GM + WM) of 9.61E5 ± 1.06E5 mm\(^3\), a mean total GM volume of 5.50E5 ± 0.65E5 mm\(^3\), a mean total WM volume of 4.11E5 ± 0.36 mm\(^3\) and a mean total WMH volume of 10.63E3 ± 16.04E3 mm\(^3\) (Table 1). This is similar to brain volume data for the whole MAS cohort (15). Table 2 shows old age and higher physiological fall risk (PPA) were associated with a smaller GM and WM volume ratios (\( p < .01 \)), but not with WMH volume ratios. More concern about falling (FES-I) was only associated with a smaller GM volume ratio.

Neuroanatomical correlates of FES-I scores are shown in Table 3. After adjusting for age, gender, ICV, scanner, and CVR, left cerebellum, left/right inferior occipital gyrus (Brodmann area [BA] 18, 19), right/left superior frontal gyrus (BA 9), and left supplementary motor area (BA 32) showed a decrease in GM volume in association with FES-I scores (Figure 1, Table 3). Neuroanatomical correlates of GAS and PPA scores showed no overlap between neuroanatomical correlates of FES-I scores. PPA scores were negatively associated with GM volumes of left premotor cortex (BA 6; voxels-in-cluster = 674; \( p = .013 \)). GAS scores were negatively associated with GM volumes of left inferior temporal gyrus (BA 20; voxels-in-cluster = 415; \( p = .005 \)) and left premotor cortex (BA 6; voxels-in-cluster = 1,302; \( p = .006 \)). There was a partial overlap between neural networks related to FES-I scores and those related to neuroticism. Neuroticism was negatively associated with reduced GM volumes in (i) right cerebellum (voxels-in-cluster = 1,619; \( p = .001 \)), (ii) left superior occipital gyrus (BA 19), left inferior temporal gyrus (BA 20), left/right temporal pole (BA 38) (voxels-in-cluster = 12,656; \( p < .001 \)), (iii) left/right medial superior frontal gyrus (BA 8; voxels-in-cluster = 5,100; \( p < .001 \)), (iv) right middle frontal gyrus (BA 9) and right premotor cortex (BA 6) (voxels-in-cluster = 1,686; \( p = .001 \)).
In order to further elucidate whether physical fall risk (PPA), vision (MET), or psychological (GAS, neuroticism) measures explain neuroanatomical correlates of concern about falling (Figure 1), we performed four additional correlation analyses. Repeated VBM analyses with separate adjustments for PPA scores and MET did not alter the results. After additional adjustment for GAS scores, only left cerebellum, left/right inferior occipital gyrus, right superior frontal gyrus, and left supplementary motor area remained negatively associated with the FES-I scores (p < .001). Additional adjustment for neurotic personality traits removed all suprathreshold GM correlates.

### Discussion

In this large cohort study of healthy older community-dwelling men and women, we observed significant associations between concern about falling and brain volumes. These findings build on those by Davis and coworkers, who found that falls efficacy is independently associated with both total brain and GM volume in a sample of older women (13). The current study is the first study that looked at the association of reduced regional GM volume and concern about falling. Therefore, we considered that an unbiased VBM analysis was most appropriate not to overlook regions of interest. Our results showed significant associations between concern about falling and GM volume in the left cerebellum, bilateral inferior occipital gyrus, bilateral superior frontal gyrus, and left supplementary motor area. Additional analyses elucidated that the association between concern about falling and reduced brain volumes was explained by neuroticism and anxiety, and not by physical fall risk or vision (Figure 1).

### Influence of Physical Fall Risk and Impaired Vision

Our study suggests that the relationship between concern about falling and regional GM decline is independent of the presence of an actual (instability-related) fall risk, as estimated by the PPA. Balance and gait are complex functions requiring coordination between multiple cortical regions that include motor areas, frontal lobe, and cerebellum in addition to subcortical structures (10,13). Balance and gait, therefore, rely on the integrity of networks not only involved in motor functions, but also in cognitive processing and executive functioning, particularly in prefrontal regions (10). It has been suggested that older people might have to use wider brain networks to compensate for age-related sensory loss to maintain balance. While our analyses confirmed associations between reduced GM volumes in regions related to motor control, we could not see an overlap between the neural networks related to concern about falling and those related to PPA scores. Furthermore, the associations between concern about falling and reduced regional GM volumes remained significant when PPA scores were included in the analysis. We acknowledge, however, that small reductions in regional brain volume might lead to reduced coordination and subtly impaired balance, especially when undertaking dual or more complex motor tasks (10), which might not be manifested in the composite PPA measure. Some of the associations between concern about falling and GM were seen in the left hemisphere only. It has been suggested that the left supplementary motor area is important for sequencing of movement (25) and the left cerebellar hemisphere is involved in visuospatial processing (26). Our study also showed an association...
between concern about falling and reduced occipital GM volumes, involved in visual processing and visual perception (27), which could not be explained by an ocular vision problem. The occipital–parietal circuit is especially important to maintain balance in people with (age-related) sensory loss. While this circuit relies primarily on visual input, it can provide additional reference frames based on other sensory inputs (28). Occipital–parietal disturbance might therefore impair remapping of the neuronal circuitry in the dorsal streams of visuospatial processing (29), and impact how other brain areas work together to maintain balance in more challenging situations. More research is required to understand this relationship.

Influence of Generalized Anxiety and Neuroticism

Considering the importance of frontal lobe and the additional role of the cerebellum for emotional processing and emotion regulation (12), the association between concern about falling and the bilateral superior frontal gyrus and left cerebellum might be due to a presence of generalized anxiety. Even though we could not see an overlap between the neural networks related to concern about falling and those related to anxiety, we did find that after controlling for generalized anxiety, the association between concern about falling and frontal lobe areas was no longer significant. This suggests that the presence of generalized anxiety symptoms might partially explain the association between concern about falling and regional GM decline. Controlling for neurotic personality traits removed all significant associations between concern about falling and GM volumes. The impact of neuroticism on the association between reduced GM volumes and concern about falling can also be confirmed in the identified overlap of neural networks in occipital regions, middle/superior frontal areas, and cerebellum in the current study. This is in accordance with previous studies that have suggested that these structures are part of a neural network recruited to process emotional information (30). Furthermore, it has also been suggested that anxiety, worry, and neurotic personality traits can lead to age-related neurodegeneration and reduced neuronal plasticity through both stress and physical inactivity (11). Therefore, it is plausible that the effects of possibly lifelong increased stress levels, which then express themselves in old age as concern about falling (as well as anxiety and neuroticism), lead to reduced brain volume. An impaired emotional–motor–cognitive network could result in a misinterpretation or exaggeration of a prior fall event or misperception of actual (instability-related) fall risk, which would ultimately transduce as concern about falling.

On the other hand, we did not see an association between concern about falling and reduced GM volumes in amygdala–hippocampal areas. The hippocampus and amygdala are particularly prone to neuronal cell loss as a result of stress and help to interpret whether an event or situation is threatening (14). Future studies should explore the association between concern about falling and amygdala–hippocampal areas further.

Study Limitations

We would like to acknowledge certain limitations as part of this study. First, it is well known that VBM has difficulties with the spatially normalizing and segmenting of atypical brains, which may result in group-specific misregistration and problems regarding the accurate localization of regional volumes (31). On the other hand, VBM has been useful to localize regional differences in GM in an unbiased manner and was therefore chosen for this exploratory study. Second, our assessment did not include a detailed measure of gait or visual processing, which could have further enhanced our understanding of the underlying mechanisms explaining the association between concern about falling and reduced regional GM volume. Third, our study sample comprises healthy, community-dwelling older people, which might not be representative of the general older population.

Conclusion and Directions for Future Research

We found concern about falling is negatively associated with total brain volume and GM volume in a large sample of older men and women, thus confirming previous findings. The current analyses suggest that concern about falling was linked to reduced GM volumes in
areas important for emotional control, and the relationship between these brain volumes and concern about falling was primarily accounted for by psychological factors (generalized anxiety and neuroticism) and not by physical fall risk factors (Figure 1). However, our results also indicated that concern about falling is linked to lower volumes in areas important for motor control, executive functions, and visual processing. Neurodegeneration of the occipital and frontal cortex (possibly as a result of lifelong stress and worry) could therefore hinder functional compensation, resulting in subtle balance impairments. While controlling for physical fall risk or vision did not alter the association between reduced GM volume in these regions and concern about falling, it is still possible that this affects balance, especially when undertaking dual or more complex motor tasks (10). This hypothesis needs to be explored further in future studies. Future studies should also explore interaction effects of physical, psychological, and cognitive factors in the relation between reduced brain volume and concern about falling, and whether previous falls affect this association.

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