White matter fibre density in the brain's inhibitory control network is associated with falling in older adults

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Abstract

Recent research has indicated that the relationship between age-related cognitive decline and falling may be mediated by the individual's capacity to quickly cancel or inhibit a motor response. This longitudinal investigation demonstrates that higher white matter fibre density in the motor inhibition network paired with low physical activity was associated with falling in elderly participants. We measured the density of white matter fibre tracts connecting key nodes in the inhibitory control network in a large sample (n=414) of older adults. We modelled their self-reported frequency of falling over a four year period with white matter fibre density in pathways corresponding to the direct and hyperdirect cortical-subcortical loops implicated in the inhibitory control network. Only connectivity between right Inferior Frontal Gyrus and right Subthalamic Nucleus was associated with falling as measured cross-sectionally. The connectivity was not, however, predictive of future falling when measured two and four years later. Higher white matter fibre density was associated with falling, but only in combination with low levels of physical activity. No such relationship existed for selected control brain regions that are not implicated in the inhibitory control network. The direction of this effect was counterintuitive and warrants further longitudinal investigation into whether white matter fibre density changes over time in a manner correlated with falling, and mediated by physical activity.

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Recent research has indicated that the relationship between age-related cognitive decline and falling may be mediated by the individual's capacity to quickly cancel or inhibit a motor response. This longitudinal investigation demonstrates that higher white matter fibre density in the motor inhibition network paired with low physical activity was associated with falling in elderly participants. We measured the density of white matter fibre tracts connecting key nodes in the inhibitory control network in a large sample (n=414) of older adults. We modelled their self-reported frequency of falling over a four year period with white matter fibre density in pathways corresponding to the direct and hyperdirect cortical-subcortical loops implicated in the inhibitory control network. Only connectivity between right Inferior Frontal Gyrus and right Subthalamic Nucleus was associated with falling as measured cross-sectionally. The connectivity was not, however, predictive of future falling when measured two and four years later. Higher white matter fibre density was associated with falling, but only in combination with low levels of physical activity. No such relationship existed for selected control brain regions that are not implicated in the inhibitory control network. The direction of this effect was counterintuitive and warrants further longitudinal investigation into whether white matter fibre density changes over time in a manner correlated with falling, and mediated by physical activity.

Keywords: Ageing, Falling, inhibitory control, DTI, white matter, physical activity

1. Introduction

It is now well established that as higher order cognitive abilities decline with ageing, the incidence of falling increases proportionally (Amboni et al., 2013; Ambrose et al., 2013; Herman et al., 2010; Kearney et al., 2013; Li et al., 2018; Mirelman et al., 2012; Montero-Odasso et al., 2012; Muir et al., 2012). However, the structural and functional neural mechanisms underlying this relationship remain undefined. In-depth behavioural testing has revealed that inhibitory control, a specific facet of executive function, is especially predictive of falling. In a longitudinal study, Mirelman et al., (2012) demonstrated that an individual's capacity for effective inhibitory control measured by computerised tests was predictive of fall prevalence in the subsequent 5 year period. This suggests that response inhibition, the ability to suppress highly automatic action in situations where such instinctive action is unwarranted (Fuster, 2008), may play a significant role in fall prevention. Furthermore, response inhibition is closely related to cognitive flexibility or the ability to adapt to complex and rapidly changing environments (Diamond, 2013) which correlates with fall prevalence (Kearney et al., 2013; Pieruccini-Faria et al., 2019). While the ability to stop may seem an unusual prerequisite for effective balance control, we often need to rapidly adapt our posture while navigating real-world settings. This entails occasional but appropriate suppression and revision of reflexive movements.

Many factors contribute to maintaining postural equilibrium such as strength (Okubo et al., 2022; Pijnappels et al., 2008), sensory acuity (Brown et al., 2015; Reed-Jones et al., 2013), blood pressure regulation (Kenny et al., 2017), and cognitive ability Mirelman et al. (2012), and this makes it difficult to ascribe a particular role to any one culprit leading to a fall. Several studies have attempted to tease out the relative contribution of convergent factors that affect fall risk, including the influence of distinct cognitive abilities. For example, Holtzer et al. (2007) studied if specific cognitive abilities were related to falls in a large sample of community dwelling older adults without cognitive impairment while also accounting for gait abnormalities (another factor related to falls (Tinetti et al., 1988). Among separate cognitive domains of verbal IQ, speed/executive attention, and memory, only speed/executive attention was related to retrospective falls. This suggested that global cognitive ability was not driving this effect (a finding consistent with Mirelman et al. (2012) where Executive Function predicted falls but overall cognitive scores were uninformative). Notably, Holtzer et al. (2007) revealed an effect independent of gait-related issues. More recently, Okubo et al. (2022) measured several standard fall-risk variables such as leg strength, postural sway, simple and choice reaction time, etc., in relation to performance on a laboratory-based perturbation paradigm where participants needed to adapt their gait to prevent a fall and the strongest predictor of balance recovery was performance on a hand-based test (ReacStick) of rapid inhibition accuracy. The aforementioned studies collectively suggest that inhibitory control plays an important role in preventing falls. This seems to be the case even when global cognitive measures fail to correlate with falls, and this role is independent of strength and general processing speed.

Beyond correlational data linking cognitive performance with falls, there have been several laboratory-based studies showing empirically how response inhibition contributes to postural equilibrium (Cohen et al., 2011; England et al., 2021; Potocanac et al., 2014; Rydalch et al., 2019; Sparto et al., 2012). The aforementioned studies focused on the execution of rapid stepping, since change-of-support reactions are often needed to regain balance (Maki & McIlroy, 1997). Older adults make more anticipatory postural adjustment errors during a choice reaction voluntary step task compared with younger adults (Cohen et al., 2011). In this case, initial acceptance of body load onto the wrong stance leg needed to first be corrected before shifting weight onto the other leg to allow the step to proceed. This led to increased choice-reaction times. Interestingly, the same study also revealed that Stroop task performance correlated with anticipatory postural adjustment errors preceding the step. The authors surmised that what may underlie an increased choice reaction time for older adults could in fact be a deficit in response inhibition versus a generic drop in processing speed due to age. Accordingly, Schoene et al. (2017) revealed that inhibitory choice reactive stepping time was associated with falls independently of reduced processing speed, lack of attention, or balance impairment. See Rey-Mermet et al. (2018), Rey-Mermet & Gade (2018), and Verhaeghen (2011) for a more nuanced discussion on the topic of inhibitory deficits and ageing.

We have recently demonstrated that performance on a balance recovery step task was correlated with speed of response inhibition in a computerised test of inhibitory control (England et al., 2021; Rydalch et al., 2019). These results, holding true for both young and older adults, suggest a common neural mechanism underlying inhibitory performance on a seated task with finger responses and a whole-body postural response to regain balance (Okubo et al., 2022).

The underlying mechanisms of response inhibition (Enz et al., 2021; Jana et al., 2020) has received much attention in the field of cognitive psychology in a wide range of disorders (Penadés et al., 2007; Slaats-Willemse et al., 2003; Whelan et al., 2012). Using neuroimaging three underlying neural networks of response inhibition have been identified: the right inferior frontal cortex (rIFC), the presupplementary motor area (preSMA), and the subthalamic nucleus (STN) (Aron et al., 2007; Aron & Poldrack, 2006; Swann et al., 2012). Coxon et al. (2012) demonstrated that these nodes, and the strength of connectivity between them, are related to performance on response inhibition tasks. They showed that the integrity of white matter connections between the rIFC and the STN predicted response inhibition task performance and so did tract strength between preSMA and STN, but only in older adults.

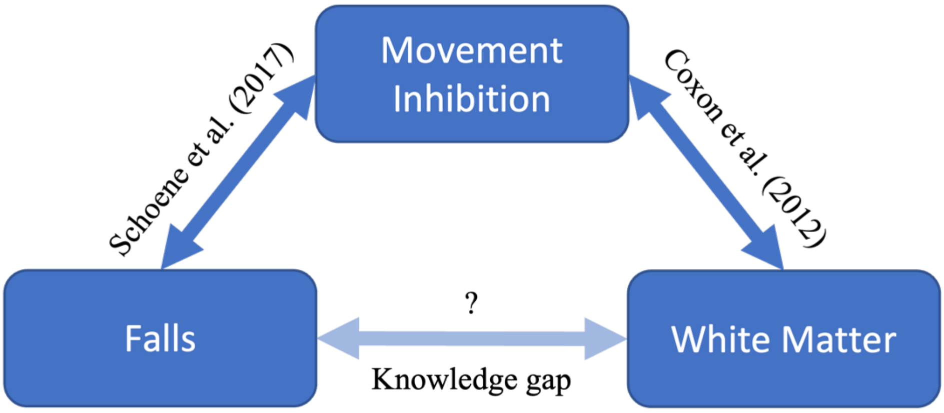


Figure 1. Theoretical framework. Schoene et al. (2017) have shown that improved performance on movement inhibition tasks are associated with a reduced number of falls in the real world. Coxon et al (2012) have shown that better performance on movement inhibition tasks is associated with higher fractional anisotropy (FA) in right IFC and stronger connectivity between left preSMA and left STN, only in older adults. We therefore tested whether individuals who fall less may show stronger white matter microstructure in the regions identified as key nodes for inhibitory control.

The theoretical framework has been outlined in Figure 1. We hypothesise that there will be an association between white matter structures related to the motor inhibition network (STN, preSMA, and right Inferior Frontal Gyrus - rIFG) and real world falls. The present study makes use of an extensive data set from the Irish Longitudinal Study on Aging (TILDA), which is a large-scale, longitudinal study with data on cognitive function, socioeconomic status, education, health history and many other variables to provide insight into the aging process from a broad perspective. Brain scans were collected from a subgroup (n=519) of TILDA participants. These scans were used to analyse white matter microstructural integrity between established nodes in the neural stopping network and determine if this was related to self-reported falls. We predicted that individuals with diminished connectivity between these specific networks would be more likely to experience falls. Overall, this study aims to provide insight into the neural mechanism underlying a specific cognitive ability - inhibitory control - and its relationship with fall prevalence in older adults.

2. Materials & methods

2.1 Participant recruitment

TILDA is a prospective, longitudinal cohort study that collects health, economic and social data from a nationally representative sample of community-dwelling Irish residents aged 50 and over (Kearney et al., 2013). Ethical approval for the TILDA study was obtained from the Faculty of Health Sciences Research Ethics Committee the Trinity College Dublin Research Ethics Committee. Signed informed consent was obtained from all respondents prior to participation. Additional ethics approval was received for the MRI sub-study from the St James's Hospital/Adelaide and Meath Hospital, Inc. National Children's Hospital, Tallaght (SJH/AMNCH) Research Ethic Committee, Dublin, Ireland. Those attending for MRI were also required to complete an additional MRI-specific consent form.

We analysed participant data collected at waves 3, 4 and 5 of the study. The data collection waves are approximately two years apart. Wave 1 was collected in 2009-2010, wave 2 was collected in 2012, wave 3 was collected in 2014-2015, wave 4 was collected in 2016, and wave 5 was collected in 2018. A collection for wave 6 is currently ongoing.

Neuroimaging data was collected at wave 3 (Whelan & Savva, 2013). Of all participants attending the wave 3 health assessment centre, a random subset were invited to return for multi-parametric brain MRI at the National Centre for Advanced Medical Imaging (CAMI) at St James's Hospital, Dublin. Participants with Mild Cognitive Impairment and stroke may exhibit different fall profiles to those noted for typically ageing individuals and introduce additional heterogeneity (Campbell & Matthews, 2010; Härlein et al., 2009; Lamb et al., 2003; Sheridan & Hausdorff, 2007; Simpson et al., 2011). Therefore, we excluded participants with MOCA (< 20) or MMSE (< 24) scores at wave 3, and additionally individuals with history of stroke or occurrence of stroke between data collection waves in the analysis.

Demographic variables applied as control variables in the models are presented in Table 1. They include age, sex, medical history (Education levels, physical disability, Blood Pressure, and polypharmacy), (Donoghue et al., 2018).

2.2 MRI protocol.

Participants were briefed on the MRI protocol ahead of acquisition, which comprised a variety of scans including structural T1 weighted images and Diffusion Weighted Imaging (DWI) sequences. Scans were acquired via 3T Philips Achieva system and 32-channel head coil.

For the T1 3D Magnetisation-prepared Rapid Gradient Echo (MP-RAGE) sequence the acquisition parameters were: FOV (mm): 240 x 240 x 162; voxel size (mm): 0.8 × 0.8 × 0.9; SENSE factor: 2; TR: 6.7 ms; TE: 3.1 ms; flip angle: 8°; acquisition time 5:24 minutes. Diffusion Weighted Images (DWI) were acquired with 66 slices in transverse plane with field of view 244 x 244 x 140mm; voxel size (mm): 1.9 × 1.9 × 2.0; SENSE factor 2; TR: 12887 ms; TE: 55 ms; flip angle: 90°; Diffusion was measured along 61 noncollinear directions (b = 1200 s/mm^2) preceded by a non-diffusion - weighted volume (reference volume, b = 0 s/mm2). Total DWI acquisition time was 17:31 minutes.

2.3 DTI pre-processing

DWI data were processed using ExploreDTI (Leemans et al., 2009). Images were corrected for subject motion and eddy currents using the procedure described in Leemans & Jones (2009). Tensor estimation was performed using the iteratively reweighted linear least-squares approach (Veraart et al., 2013). Fibre trajectories were computed with CSD based tractography (Tournier et al., 2007) using recursive calibration of the response function to optimise the estimation of the fibre orientation distribution (FOD) functions (Tax et al., 2014). A uniform grid of tractography seed points at a resolution of 2 x 2 x 2 mm^3 was used with an angle threshold of 30 degrees, an FOD threshold of 0.1, and maximum harmonic order of eight. The median number of streamlines computed for each participant was 55,221 (IQR 8665). A restricted tractography analysis was performed subsequently to reconstruct streamlines passing through pairs of ROIs that form part of the Shen 268 atlas (Shen et al., 2013). Reconstructed fibre trajectories for each individual were quantified in terms of the (median) fractional anisotropy (FA), Apparent Fibre Density (AFD), mean diffusivity (MD), and radial diffusivity (RD), which are all measures that reflect the directional coherence of intracellular water diffusion. Using Constrained Spherical Deconvolution for tractography rather than the traditional diffusion tensor model allows calculation of the Apparent Fibre Density (AFD), a measure of microstructural white matter integrity that performs better than standard Fractional Anisotropy (FA) in regions with densely crossing fibres (Dell'Acqua & Tournier, 2019). As AFD provides a superior measure, we focussed our inferential statistics on this metric, but have provided comparable results with FA in the supplementary material for completeness and to allow comparison with previous research studies.

2.4 Statistical Analysis Demographic Variables

Statistical analysis of the demographic variables at wave 3 were performed using independent two-sample t-tests for age, sex, disability and number of medications, and chi-square tests for the variables education, hypertension, and physical activity.

2.5 Logistic Regression

A logistic regression model was used to investigate the association between white matter structures connecting selected regions of interest (ROI) and whether older individuals reported falling. The model was created in RStudio (RStudio Team, 2022). For each ROI a logistic model was generated. The binary dependent variable was whether participants had a fall (1) or did not fall (0) between wave 3 (2014-2015) and wave 5 (2018). The independent variables of interest were the respective measurements of reconstructed fibre trajectories for each ROI-ROI pair. There were 6 independent control variables: Age, Sex, Education, Number of Medications (Polypharmacy), Blood pressure, and a measure of physical disability. The following paragraphs will describe elements of the model and add a rational for including them.

2.5.1 Regions of Interest

The Shen 268 atlas was used (Figure 2A-D), which is a parcellation of the brain into 268 areas based on resting functional state data (Shen et al., 2013). We selected 5 ROIs representing the movement inhibition network: the right inferior frontal gyrus (rIFG), the left and right subthalamic nuclei (r/l STN), and the left and right presupplementary motor area (r/l preSMA, see Figure 2 E-I). All ROIs except the IFG consisted of individual shen atlas ROIs. However, the IFG ROI consists of 3 individual shen atlas ROIs. Therefore, results involving the IFG will be further analysed by looking that the individual ROIs.

The tractographies were conducted between the r/l STN and the other ROIs (rIFG, r/l preSMA), or between the individual ROIs of the IFG and the r/l STN, resulting in 6 comparisons every time. Therefore, the significance threshold was adapted using a Bonferroni correction for six tests yielding a new critical alpha of 0.0083.

The tractography was conducted in a hypothesis driven manner between restricted pairs of nodes based upon structural networks known to mediate inhibitory control (Table 2). To allow for comparisons between ROIs, the AFD values were z-transformed.

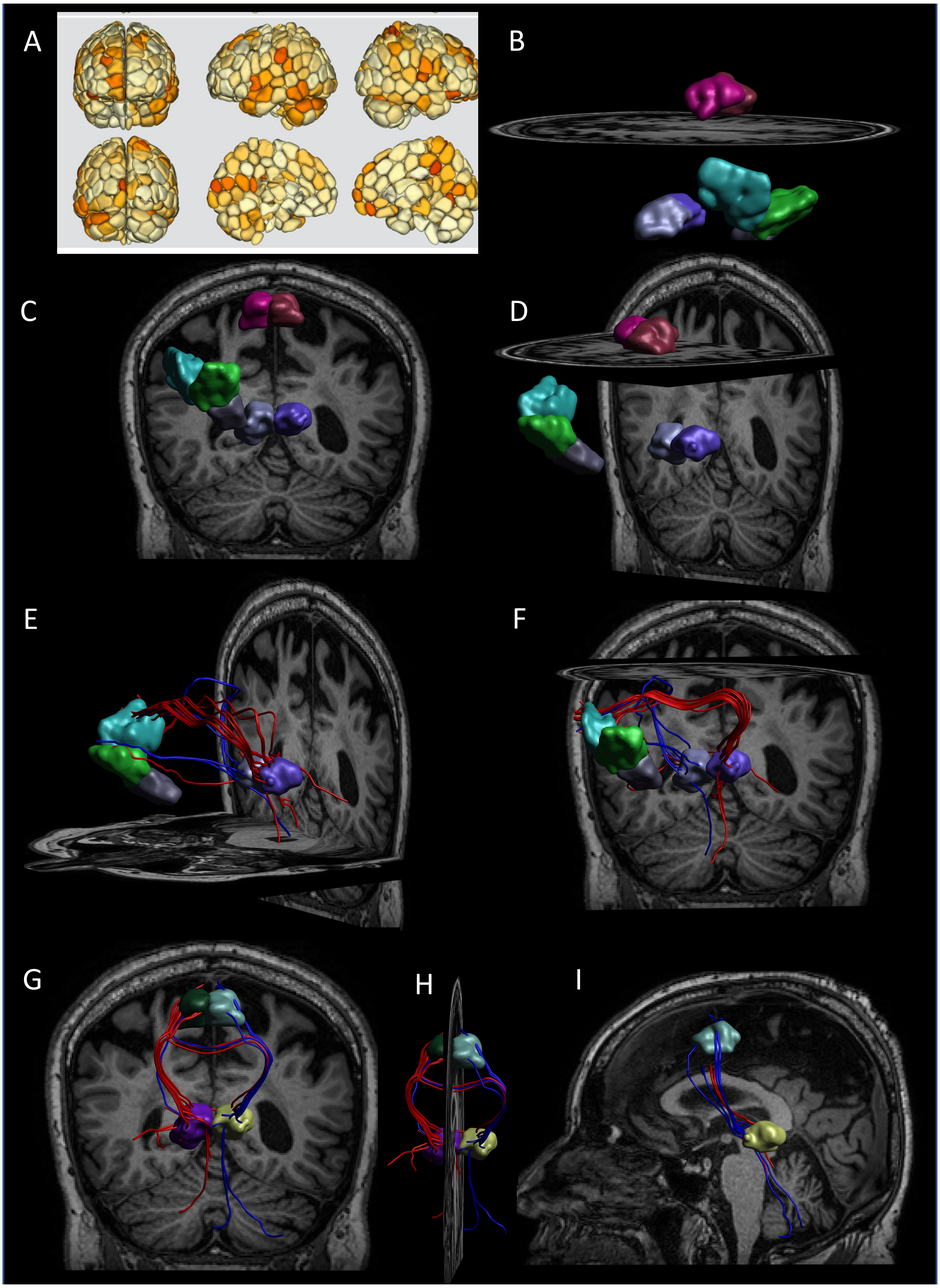


Figure 2. Regions of Interest and Reconstructed Streamlines. Panel A shows the Shen atlas parcellation that was used, with ROIs shown in Panels B-D selected for analysis. Panels E-F show different viewpoints of the ROIs with reconstructed streamlines passing between right and left STN and right IFG for one representative participant. Panels G,H and I show different viewpoints of reconstructed streamlines passing between bilateral STN and preSMA.

2.5.2 Control Analysis

As an additional experimental control a separate tractography analysis between selected control regions and the r/l STN was performed. As a control region for the rIFG, the left IFG was chosen for topographical similarity but different functionality (Amunts & Zilles, 2012; Aron et al., 2014; Deng et al., 2017; Du et al., 2020). For the r/l preSMA control region, we chose the r/l FFA as a pair of symmetrical areas not related to movement inhibition (Burns et al., 2019). Table 1 in the supplementary material describes the ROI characteristics.

2.5.3 Control variables

We included 6 control variables known to influence fall rates in our original logistic regression model: Age, Sex, Education, Blood Pressure, Disability Score and Polypharmacy. An additional variable of physical activity was added for the post-hoc analysis of the results. Age is known to increase fall rate and was left untransformed as a numerical value (Chang et al., 2015; Deandrea et al., 2010; Franse et al., 2017; Karlsson et al., 2013). Female sex increases the severity of falls due to more prevalent osteoporosis and may increase fallrate, although the findings on the latter are inconsistent (Deandrea et al., 2010; Franse et al., 2017; Karlsson et al., 2013). Education is known to correlate with a wide array of neurologically relevant characteristics. Education serves as an indirect measurement of socioeconomic status aside from its protective effects against neurodegeneration. Both socioeconomic status and neurodegenerative processes have been discussed in their relation to falls in the older population (Khalatbari-Soltani et al., 2021; Then et al., 2016). In the linear models education was coded as a numeric variable with numbers 1-3 for primary, secondary and tertiary education.

Blood Pressure (BP) measurements were categorised after clinical criteria. For Systolic BP the four thresholds were: Normal <120, Elevated < 130, Hypertension 1 < 140, Hypertension 2 > 140 , and for Diastolic the four thresholds were: Normal <80, Elevated < 80, Hypertension 1 < 89, Hypertension 2 > 90. If an individual presented two different categorisation for systolic and diastolic blood pressure, the higher BP category was chosen. High blood pressure may protect against falls caused by syncope due to low blood pressure (Butt et al., 2012), however, contradictory results exist (Ha et al., 2021).

Physical disabilities are known to increase fall rates. Our disability score, recorded in TILDA as a series of 11 self-reported yes or no questions asking if the respondant has difficulty performing certain tasks (e.g. “Do you have difficulty walking 100m?”, or “Do you have difficulty walking up 1 flight of stairs without resting”), was summed for each participant resulting in a score of 1-12 (Deandrea et al., 2010; Ha et al., 2021). Different types of drugs, such as antihypertensives, antiepileptics, sedatives and psychotropics are known to affect fall rate. Therefore, the number of medicines used by a participant was included in the model as measure of medicinal drug use (Bloch et al., 2011; Deandrea et al., 2010; Hartikainen et al., 2007).

For an additional analysis the variable of physical activity was used. Physical activity was coded per the IPAC standard (Craig et al., 2003). The IPAC asks participants to note the amount of time they spent doing vigorous, moderate or walking activities and gives them different weights to calculate a score and categorise participants into high, moderate and low physical activity.

2.5.4 Predictive Model

For the logistic model aiming to predict future falling, fallers at wave 3 were removed, and fallers at wave 4 and 5 were aggregated and labelled “fallers after wave 3”. Other parameters were the same as for the cross-sectional model.

3. Result

3.1 Demographics

Fallers had a significantly higher number of disabilities t(412)= 2.3738 , p= 0.018, and a significant difference in the proportion of blood pressure categories between groups, $X^2(3)$ = 17.0452, p= 0.00069. The significant result for blood pressure is driven by hypertension 1. Without Hypertension 1 the result loses significance $X^2(2)$ = 0.25, p= 0.88.

3.2 Prevalence of Falling

For the cross-sectional analysis our criteria resulted in the inclusion of 414 participants that underwent MRI acquisition at wave 3. Ninety seven of the 414 participants at wave 3 reported

Table 1

Demographic variables of selected participants at wave 3

			Fallers W3 (n = 97)	Nonfallers W3 (n = 317)	p-Value
Age		Mean (sd)	69.21 (8.23)	68.2 (7.39)	0.2524[b]
Sex	Male	n (%)[a]	42 (43.3)	158 (49.8)	0.31[c]
	Female	n (%)[a]	55 (56.7)	159 (50.2)	
Education					0.29[c]
	Level 1	n (%)[a]	22 (22.7)	51 (16.1)	
	Level 2	n (%)[a]	36 (37.1)	119 (37.5)	
	Level 3	n (%)[a]	39 (40.2)	147 (46.4)	
Disability		Mean (sd)	2.05 (1.88)	1.58 (1.65)	0.018[b]
Blood Pressure					0.00069[c]
	Normal	n (%)[a]	25 (25.8)	69 (21.8)	
	Elevated	n (%)[a]	16 (16.5)	39 (12.3)	
	Hypertension 1	n (%)[a]	10 (10.3)	99 (31.2)	
	Hypertension 2	n (%)[a]	46 (47.4)	110 (34.7)	
Number of Meds		Mean (sd)	2.94 (2.34)	2.5 (2.52)	0.13[b]
Physical Activity		n	92	302	0.21[c]
	Low	n (%)[a]	35 (38.0)	106 (35.1)	
	Moderate	n (%)[a]	40 (43.5)	113 (37.4)	
	High	n (%)[a]	17 (18.5)	83 (27.5)	

Table 1. Table showing the basic demographic variables of participants at wave 3 selected for this study. Participants were grouped into fallers and nonfallers. [a] Valid percent [b] Independent two-sample t-test [c] Chi-square test over all levels and categories.

having fallen since the last interview. For the predictive analysis our criteria resulted in the inclusion of 317 participants of which 96 fell between waves 3 and 4, or between waves 4 and 5.

3.3 Associative (cross-sectional) logistic regression results

The results of the cross-sectional logistic regression are depicted in Table 2. The model using the AFD values between the rIFG and rSTN achieved a p value of 0.005. This implies that an increase in AFD of 1 standard deviation in the tracts connecting rIFG and rSTN significantly increased the odds of falling by 1.49 (CI: 1.13, 1.98).

Table 2:

Association between microstructural integrity in inhibitory control networks and odds of falls in elderly.

Region	Odds	CI Low	CI High	P Value	Chi Square Fit	n
r IFG - r STN	1.49	1.13	1.98	**0.005**	0.00003	360
l preSMA - r STN	1.38	0.93	2.05	0.113	0.00046	200
r IFG - l STN	1.28	0.91	1.8	0.161	0.00172	237
r preSMA - r STN	0.84	0.61	1.16	0.288	0.02334	257
r preSMA - l STN	0.91	0.65	1.26	0.557	0.00976	228
l preSMA - l STN	0.97	0.73	1.29	0.855	0.00096	343

Table 2. Results of a logistic regression showing the association between the tractography of ROIs and the risk of falling in older people. A single result (r IFG to r STN) is significant after correcting for multiple comparisons (Bonferroni, new p threshold: 0.0083), in bold. The Chi Square and number of observations in the model are included.

The model fulfilled all assumptions for a logistic regression (see supplementary material 5.2). A Chi square fit showed that the model was a good fit for the data ($x^2 = 0.00003$), and the McFadden R^2 Improved from 0.054 (model without AFD) to 0.094 by including the variable of interest. An additional observation is that the control variable blood pressure with category hypertension 1 significantly decreased the odds of falling by 0.18 (CI: 0.065, 0.48, p-value: 0.00067) (Figure 3).

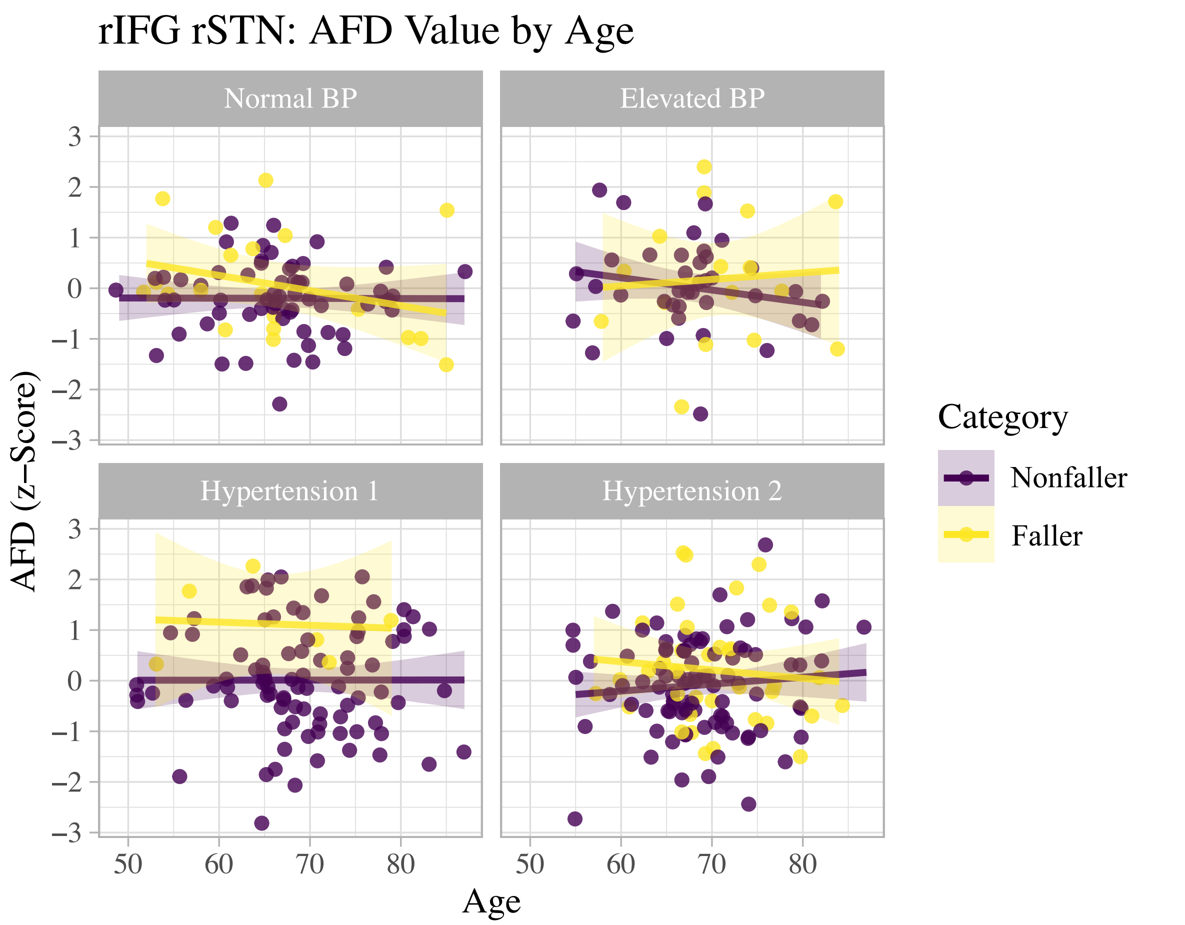


Figure 3. Figure 3 shows rIFG – rSTN fibre density (AFD) by Age, separated by Blood Pressure categories, with separate lines for fallers and nonfallers . There were significantly less fallers in the 'Hypertension 1' category. In the cohort with normal blood pressure, there are a total of 84 participants, 21 (25%) of which fell. For elevated blood pressure there are a total of 54 participants, 16 (29.63%) of which fell. For hypertension 1 there are a total of 93 participants, 6 (6.45%) of which fell. For hypertension 2 there are a total of 129 participants, 37 (28.68%) of which fell.

Figure 4A shows that older individuals who fell (M = 0.23, SD = 1.1) had higher AFD values in the white matter pathways connecting rIFG to rSTN (Nonfallers M = -0.066, SD = 092, directional Wilcoxon Rank Sum test, W = 9716, p= 0.035). This effect was most pronounced in the 50-65yr old fallers, as AFD values appeared to be lower in the older 65+ fallers. Nonfallers show no such trend in AFD values cross sectionally over the age range. We investigated this post hoc by adding an age-AFD interaction term to the rIFG-rSTN model. The age-AFD interaction term did not reach significance, reducing odds of a fall by 0.038 (CI: 0.072, 1.28, p= 0.058) while the AFD term was still significant, increasing the odds of a fall by 21.87 (CI: 16.47, 29.04, p= 0.03). The increase in odds for the rIFG to rSTN AFD value is mathematically inflated in the model with the interaction term, as the value features twice in the model as part of the interaction and main effect. It is also further inflated due to the comparatively high numeric range of age.

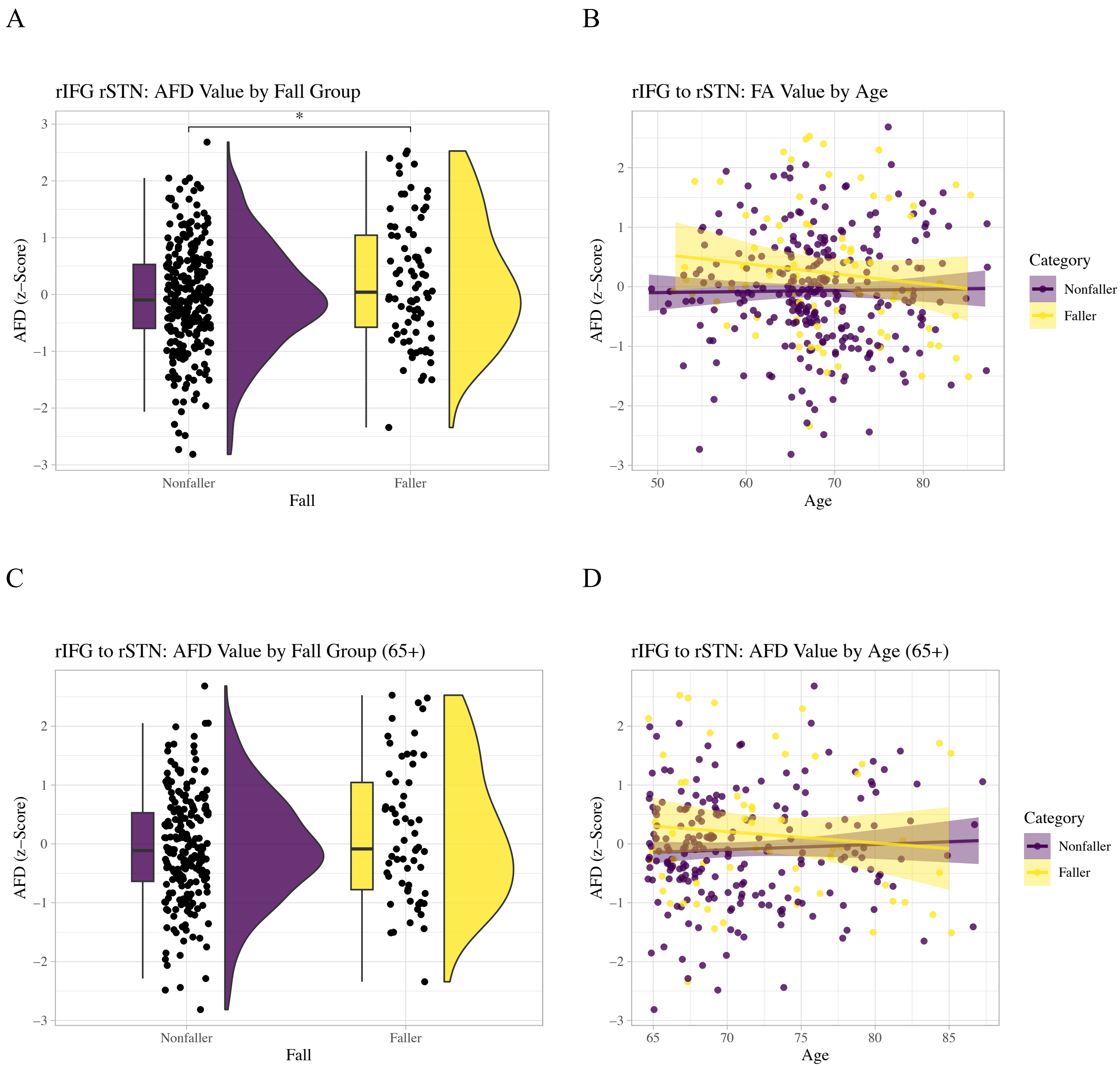


Figure 4. Figure A shows differences in the distribution of fallers vs nonfallers. Fallers seem to have overall higher AFD values. Figure B shows the difference in distribution according to age. Fallers also have a higher average AFD value, although this relationship is dependent on age. Figure C and D show the difference in distribution of fallers, but only including fallers of age 65 or more.

Constraining the analysis to individuals aged 65 + has no effect on the overall distribution (Figure 4 C & D). However, no significant results were found using a sample of people aged 65 or more – likely due to the reduced sample size.

3.3.1 Interaction with physical activity

Table 3:

Association between microstructural integrity in inhibitory control networks and odds of falls in older adults.

Region	Odds	CI Low	CI High	p-Value	Chi Square Fit	n
rIFG - r STN	2.31	1.42	3.78	**0.00082**	0.000061	360
l preSMA - r STN	1.31	0.74	2.3	0.35	0.0098	200
l preSMA - l STN	1.23	0.76	2	0.41	0.0037	343
r preSMA - l STN	0.8	0.43	1.49	0.48	0.041	228
r preSMA - r STN	0.83	0.47	1.47	0.53	0.1	257
rIFG - l STN	1.06	0.61	1.86	0.83	0.0083	237

Table 3. Results of a logistic regression showing the association between the tractography of ROIs and the risk of falling in older people when accounting for physical activity. A result (r IFG to r STN) is significant after correcting for multiple comparisons (Bonferroni, new p threshold: 0.0083), the pis bold. The Chi Square and number of observation of the model are included.

We hypothesized that higher AFD values indicative of dense white matter connectivity in older people would be associated with lower risk of falling. However, this relationship was not found in our data – instead, we found that higher AFD led to increased fall risk. We investigated this relationship deeper, hypothesizing that more active older people may be generally healthier and have higher AFD values, and be more likely to fall due to greater physical activity than their sedentary counterparts.

Adding an interaction between physical activity level and AFD values to the model required the inclusion of a main effect term. Therefore, the updated logistic regression model contained two new elements; a term for physical activity and the term for the interaction between physical activity and AFD values.

The results of the cross-sectional logistic regression are depicted in Table 3. The model using the AFD values between the rIFG and rSTN achieved a p value of 0.00082. This means that an increase in rIFG - rSTN AFD by 1 standard deviation significantly increased the odds of falling by 2.31 (CI: 1.42, 3.78). The McFadden Pseudo R squared of this model improves to 0.12 compared to a model with no AFD and no AFD * physical activity interaction.

Moderate physical activity increased the odds of falling by 1.44 (CI: 0.75, 2.75), although not significantly (p= 0.28). However, the interaction term of moderate physical activity and AFD value significantly (p= 0.014) decreased the odds of falling by 0.44 (CI: 0.22, 0.84). High physical activity does not significantly affect outcomes, neither as a main or interaction effect.

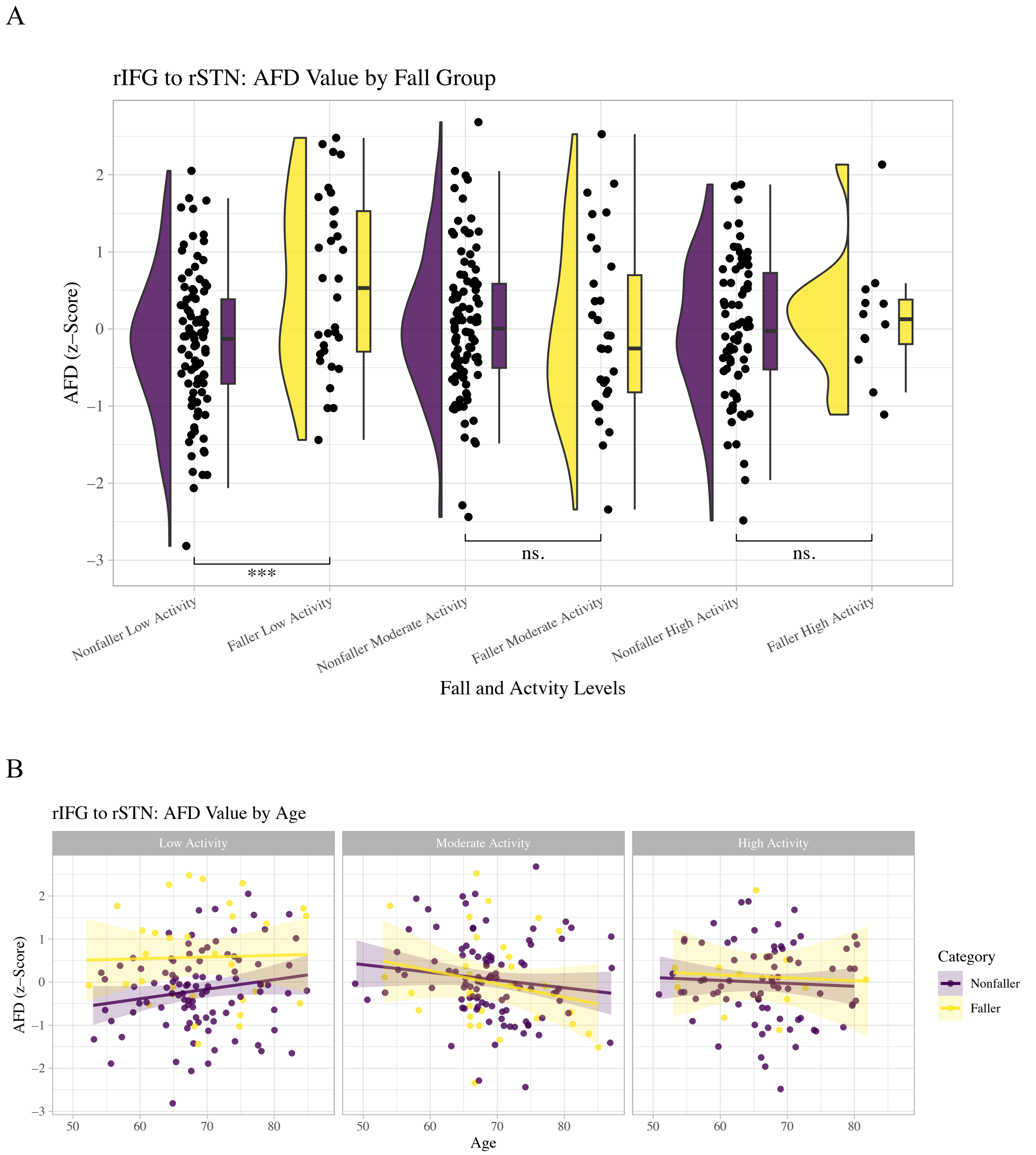


Figure 5. Panel A shows differences in the distribution of fallers vs nonfallers. Fallers have overall higher AFD values in the low activity condition, but not in high or moderate physical activity. Figure B shows the difference in distribution according to age. Fallers also have a higher average AFD value, and this relationship is less dependent on age when accounting for physical activity.

In Figure 5 it is visible that AFD is significantly ($t(125) = -3.87$, $p= 0.00018$) higher for fallers ($m = 0.58$, $sd = 1.12$; nonfallers = $m = -0.19$, $sd = 0.92$) that are not physically active, however, the same is not true for moderately active (Fallers: $m = -0.023$, $sd = 1.13$; nonfallers: $m = 0.066$, $sd = 0.92$; $t(127) = 0.44$, $p= 0.66$), or highly active older people (Fallers: $m = 0.13$, sd = 0.82; nonfallers: m = -0.007, sd = 0.9; t(86) = -0.5, p= 0.62). The data presented in Figure 5B further suggests that much of the interaction between falling and age is cleared up when the model accounts for physical activity.

3.3.1.1 ROI Subregion Analysis

Table 4:

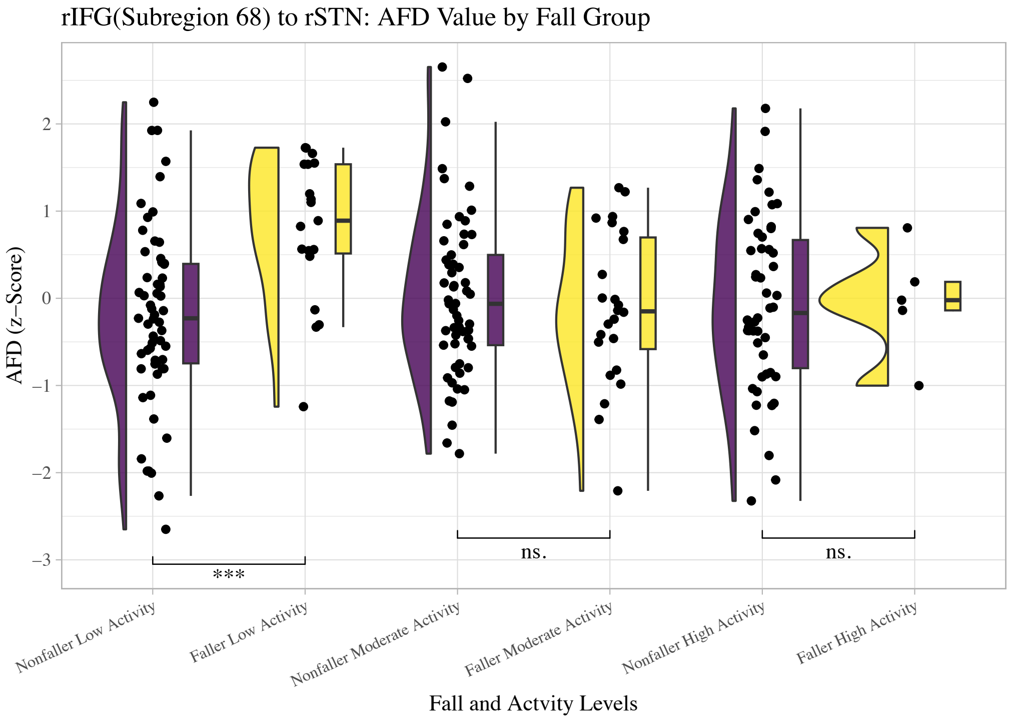
Association between microstructural integrity in inhibitory control networks and odds of falls in older adults.

Region	Odds	CI Low	CI High	p-Value	Chi Square Fit	n
rIFG (subregion 68) - r STN	3.59	1.7	7.56	**0.00079**	0.000027	221
rIFG (subregion 79) - r STN	2.08	1.06	4.05	0.032	0.007	249
rIFG (subregion 79) - l STN	1.79	0.84	3.8	0.13	0.16	130
rIFG (subregion 90) - r STN	0.58	0.28	1.19	0.14	0.21	186
rIFG (subregion 68) - l STN	1.22	0.45	3.31	0.7	0.0016	139
rIFG (subregion 90) - l STN	8.93E+21	0	-	1	0.0014	35

Table 4. Results of a logistic regression showing the association between the tractography of ROIs and the risk of falling in older people when accounting for physical activity. A result (r IFG to r STN) is significant after correcting for multiple comparisons (Bonferroni, new p threshold: 0.0083), the pis bold. The Chi Square and number of observation of the model are included.

The results of the cross-sectional logistic regression testing three further sub-divisions of rIFG are depicted in Table 4. When analysing subregions of the rIFG, one region is significant. Area 68 - R.BA.37.10 in the Shen atlas – near to the parahippocampal gyrus is significant (p= 0.00079). Increases of 1 SD of AFD in this region increases the odds of falling by 3.59 (CI: 1.7, 7.56).

A



B

Figure 6. Figure A shows differences in the distribution of fallers vs non fallers. Fallers seem to have overall higher AFD values in the low activity condition, but not in high or moderate physical activity. Figure B shows the difference in distribution according to age. Fallers also have a higher average AFD value.

Compared to the model using the whole rIFG structure, the McFadden pseudo R squared improves from 0.054 in a model with no AFD or AFD and physical activity interaction term to 0.2.

In this model, moderate physical activity significantly increased the odds of falling by 2.6 (CI: 1.05, 6.4, p= 0.038). Similarly, the interaction term of moderate physical activity and AFD value significantly (p= 0.006) decreased the odds of falling by 0.27 (CI: 0.1, 0.68). High physical activity did not significantly affect outcomes, neither as a main or interaction effect.

Looking at Figure 6 we can see that AFD is significantly ($t(76) = -3.85$, $p= 0.00025$) higher for fallers (m = 0.79, sd = 0.83; nonfallers: m = -0.21, sd = 1.03) that are not physically active, however, the same is not true for moderately active (Fallers: m = -0.12, sd = 0.88; nonfallers: m = 0.012, sd = 0.94; $t(79) = 0.59$, $p= 0.56$), or highly active older people (Fallers: m = -0.033, sd = 0.65; nonfallers: m = 0.06, sd = 1; $t(53) = -0.058$, $p= 0.95$).

3.4 Predicting future falling from structural brain data

We combined data on falling that occurred at any point following the MRI scan at wave 3 until wave 5. The results of the predictive logistic regression are depicted in table 5. AFD of white matter pathways connecting any of the aforementioned ROIs did not predict future falling at waves 4 or 5. (Table 5).

The results of the predictive logistic regression accounting for physical activity are depicted in table 6. No significant association between the independent and dependent variables were observed (Table 5).

Table 5:

Prediction of fall risk in older adults by white matter microstructure.

Region	Odds	CI Low	CI High	P Value	Chi Square Fit	n
l preSMA - l STN	1.42	1.05	1.92	0.023	0.023	265
r preSMA - r STN	0.74	0.52	1.06	0.097	0.017	200
r preSMA - l STN	0.81	0.54	1.2	0.29	0.026	171
r IFG - r STN	1.04	0.78	1.39	0.776	0.125	276
r IFG - l STN	0.97	0.66	1.42	0.861	0.330	180
l preSMA - r STN	0.98	0.69	1.4	0.926	0.387	156

Table 5. Results of a logistic regression showing the prediction of the risk of falling in older adults using Apparent Fibre Density in pathways connecting targeted ROIs. No result is significant after correcting for multiple comparisons (Bonferroni, new p threshold: 0.0083). The Chi Square and number of observation of the model are included.

Table 6:

Association between microstructural integrity in inhibitory control networks and odds of falls in older adults

Region	Odds	CI Low	CI High	p-Value	Chi Square Fit	n
r preSMA - r STN	0.43	0.22	0.84	0.014	0.039	201
l preSMA - l STN	1.55	0.93	2.58	0.09	0.14	268
rIFG - r STN	1.16	0.74	1.84	0.52	0.28	282
rIFG - l STN	0.92	0.5	1.7	0.79	0.34	186
l preSMA - r STN	1.04	0.64	1.69	0.88	0.24	158
r preSMA - l STN	1.03	0.5	2.12	0.94	0.12	173

Table 6. Results of a logistic regression showing the prediction of the risk of falling in older adults using the Apparent Fibre Density. No result is significant after correcting for multiple comparisons (Bonferroni, new p threshold: 0.0083). The Chi Square and number of observation of the model are included.

3.5 Control ROI analysis

To further guard against false positives, we also performed a control analysis using areas not directly implicated in inhibitory control. To maintain similarity with the experimental analyses, we still targeted bilateral STN, but instead of analysing the rIFG and preSMA connections to STN, we chose the FFA (Fusiform Face Area), an area generally not considered to be substantial components of the inhibitory control network. We also added the lIFG area (consisting of 3 shen ROIs). The lIFG was included to increase the validity of the control ROIs. However, as task challenge, age or impairment increase, lIFG may influence inhibitory performance (Heilbronner & Münte, 2013; Swick et al., 2008). This yielded no significant results when any of the aforementioned models were conducted with the control regions.

Voxel count (with rIFG and lIFG split up into their individual ROIs) between control ROIs (Mean = 3391, SD = 738.99) and experimental ROIs (Mean = 3919.86, SD = 899.14) did not differ significantly ($t(11.567) = 1.20$, $p = .25$).

3.5.1 Cross-Sectional Models for Control ROIs

The results of the cross-sectional logistic regression are depicted in table 3. No significant association between the independent and dependent variables were observed (Table 7).

Table 7

Association between microstructural integrity in inhibitory control networks and odds of falls in older adults.

Region	Odds	CI Low	CI High	p-Value	Chi Square Fit	n
r FFA - r STN	1.56	1.04	2.33	0.03	0.0227	178
lIFG - l STN	0.73	0.53	1	0.05	0.0001	282
lIFG - r STN	0.84	0.59	1.21	0.36	0.0042	197
l FFA - l STN	0.85	0.54	1.35	0.5	0.0050	124
r FFA - l STN	1.34	0.44	4.08	0.61	0.2286	39
l FFA - r STN	0.92	0.42	2	0.83	0.0192	70

Table 7. Results of a logistic regression showing the prediction of the risk of falling in older adults using the Apparent Fibre Density. No result is significant after correcting for multiple comparisons (Bonferroni, new p threshold: 0.0083). The Chi Square and number of observation of the model are included.

3.5.1 Predictive Models for Control ROIs

The results of the predictive logistic regression are depicted in table 8. No significant association between the independent and dependent variables were observed (Table 8).

Table 8

Association between microstructural integrity in inhibitory control networks and odds of falls in older adults.

Region	Odds	CI Low	CI High	p-Value	Chi Square Fit	n
l IFG - l STN	1.38	1	1.91	0.05	0.0015	223
r FFA - l STN	0.34	0.09	1.3	0.12	0.1150	29
r FFA - r STN	1.37	0.89	2.09	0.15	0.0081	138
l FFA - r STN	1.42	0.73	2.78	0.3	0.2500	55
l FFA - l STN	0.99	0.54	1.84	0.98	0.1232	89
l IFG - r STN	1	0.65	1.53	1	0.1557	147

Table 8. Results of a logistic regression showing the prediction of the risk of falling in older adults using Apparent Fibre Density. No result is significant after correcting for multiple comparisons (Bonferroni, new p threshold: 0.0083). The Chi Square and number of observation of the model are included.

4. Discussion

In the current longitudinal investigation we demonstrated a significant association between white matter fibre density in pathways connecting two key regions in the brain's inhibitory control network, and falling in a large sample (n=414) of older participants. We tested the microstructural integrity of white matter pathways corresponding to the direct and hyperdirect cortical-subcortical loops implicated in inhibitory control, and found that only connectivity between right Inferior Frontal Gyrus (rIFG) and right Subthalamic Nucleus (rSTN) was implicated in falling. This was observed cross-sectionally by modelling self-reported falling that had already occurred in the time period preceding structural brain measurements. The rIFG-rSTN connectivity was not, however, predictive of future falling when measured two and four years later. Further, no such relationships existed for selected control brain regions that are not implicated in inhibitory control. While statistically robust and surviving strict multiple comparison corrections, our key finding was counterintuitive as the direction of the effect was opposite to that which we hypothesised. Higher Apparent Fibre Density (AFD) values in the rIFG-rSTN pathways were associated with greater likelihood of falling. We performed post-hoc analyses to unpick the effect further, revealing that this finding was significantly influenced by physical activity levels in the older individuals. Higher AFD values only yielded higher odds of falling in combination with low levels of physical activity. In individuals with moderate or high physical activity levels, AFD had no bearing on falling.

Having a large sample size allowed us to construct a complex logistical model with falling as the dependant variable, using a set of known influences as control variables (Age, sex, education, blood pressure, polypharmacy, disabilities of daily living) and the AFD values between ROIs as independent variables. We focussed our analysis on apparent fibre density (AFD) instead of the traditionally reported FA values to measure white matter structures within the brain. AFD offers several advantages over FA, the most pertinent being increased accuracy for measuring crossing fibres tracts within voxels (Dell'Acqua & Tournier, 2019). The model reaffirmed the previous finding that high blood pressure may act as a protective factor against falls – likely by preventing falls due to syncope from blood pressure drops (Butt et al., 2012). A further strength of the study was that an investigation into control areas not related to movement inhibition yielded no significant results.

Coxon et al. (2012) initially established a relationship between right Inferior Frontal Cortex (rIFC) white matter structure and decreased response inhibition time in young and older adults. They additionally reported higher FA in white matter projections bilaterally between the IFC and STN in older (but not younger) adults with fastest response inhibition times. Schoene et al. (2017) demonstrated an association between step response inhibition and real life falls and consistent with this idea, Nagamatsu et al. (2013) found hypo-activation in prefrontal brain regions during a test of inhibitory control in individuals who fell more often. Hence, we hypothesised that greater microstructural integrity of white matter pathways in these networks may predict current and future falling. While we did detect a significant relationship, our finding that the individuals with most densely connected pathways fell more was surprising. Our approach was to use AFD in a move towards more complex models that take into account the complexity of fibre density and directionality such as AFD, and this is notably different from the method employed by Coxon et al (2012) where FA was the main measure of white matter microstructure. However, we did verify that the same pattern of results reported here holds true with FA (see supplementary material for analyses). Furthermore, while FA values generally decline with increasing age, this relationship does not apply to AFD values (Choy et al., 2020). Therefore, a complex relationship between AFD in traditional stopping networks and falling behaviour is likely. It is also possible that the higher density connectivity we detected is a structural correlate of a less efficient, diffuse signal recruiting more neural units as compensation for resources extended beyond their limits, but this is merely conjecture. Considering how older adults show more widespread brain activity compared to younger adults (Seidler et al., 2010), our results may be consistent with the theory that more effort and neural resources are required in the older brain to achieve the same task that younger brains accomplish more effortlessly.

As this was an observational study and the predictive models yielded no significant findings, we cannot infer causality or directionality in the relationship between fibre density and falling. The fact that individuals who fall tended to already have higher fibre density in inhibitory control pathways may be a cause or consequence of the falling. For example, it is conceivable that increased AFD values in fallers may be related to increased attention to balance and active learning processes subsequent to a fall, rather than bring pre-existing. Follow-up MRI scanning with the same cohort of participants may unpick this relationship further to disentangle whether changes in rIFG-rSTN microstructure drive changes in falling or vice versa.

To define this relationship further, we investigated the mediating effects of physical activity. By definition physical activity implies that people are engaging in behaviours that make falls more likely. It is therefore not surprising that physical activity itself leads to an increase in falling behaviour in our models. Interestingly there was no correlation between falling and

AFD in those with higher physical activity levels. This warrants follow-up investigation with more objective measurement methodologies as the activity levels reported in TILDA rely on self-reported activity levels within the last 7 days of interviewing, which has been shown to be subject to over- and underestimation (Lee et al., 2011; Prince et al., 2008).

5. Conclusion

Using MRI and self-reported data from 414 participants from the Irish longitudinal study on ageing we showed that higher microstructural integrity in white matter pathways connecting the right inferior frontal gyrus and right subthalamic nucleus was associated with falling in older adults. This relationship was pre-existing at the time of structural MRI data acquisition, and therefore precludes establishing causality or directionality of the effect. Fibre density at the time of MRI data collection did not predict future falling two or four years later. Follow-up MRI data will be required in order to determine whether densely connected regions in the inhibitory control network change over time in a manner correlated with falling, or whether this relationship is purely cross-sectional, and perhaps mediated by a third currently undefined factor.

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Tables

Table 1

Demographic variables of selected participants at wave 3

			Fallers W3 (n = 97)	Nonfallers W3 (n = 317)	p-Value
Age		Mean (sd)	69.21 (8.23)	68.2 (7.39)	0.2524[b]
Sex	Male	n (%)[a]	42 (43.3)	158 (49.8)	0.31[c]
	Female	n (%)[a]	55 (56.7)	159 (50.2)	
Education					0.29[c]
	Level 1	n (%)[a]	22 (22.7)	51 (16.1)	
	Level 2	n (%)[a]	36 (37.1)	119 (37.5)	
	Level 3	n (%)[a]	39 (40.2)	147 (46.4)	
Disability		Mean (sd)	2.05 (1.88)	1.58 (1.65)	0.018[b]
Blood Pressure					0.00069[c]
	Normal	n (%)[a]	25 (25.8)	69 (21.8)	
	Elevated	n (%)[a]	16 (16.5)	39 (12.3)	
	Hypertension 1	n (%)[a]	10 (10.3)	99 (31.2)	
	Hypertension 2	n (%)[a]	46 (47.4)	110 (34.7)	
Number of Meds		Mean (sd)	2.94 (2.34)	2.5 (2.52)	0.13[b]
Physical Activity		n	92	302	0.21[c]
	Low	n (%)[a]	35 (38.0)	106 (35.1)	
	Moderate	n (%)[a]	40 (43.5)	113 (37.4)	
	High	n (%)[a]	17 (18.5)	83 (27.5)	

Table 1. Table showing the basic demographic variables of participants at wave 3 selected for this study. Participants were grouped into fallers and nonfallers. [a] Valid percent [b] Independent two-sample t-test [c] Chi-square test over all levels and categories.

Table 2

Association between microstructural integrity in inhibitory control networks and odds of falls in older adults.

Region	Odds	CI Low	CI High	P Value	Chi Square Fit	n
r IFG - r STN	1.49	1.13	1.98	**0.005**	0.00003	360
l preSMA - r STN	1.38	0.93	2.05	0.113	0.00046	200
r IFG - l STN	1.28	0.91	1.8	0.161	0.00172	237
r preSMA - r STN	0.84	0.61	1.16	0.288	0.02334	257
r preSMA - l STN	0.91	0.65	1.26	0.557	0.00976	228
l preSMA - l STN	0.97	0.73	1.29	0.855	0.00096	343

Table 2. Results of a logistic regression showing the association between the tractography of ROIs and the risk of falling in older people. A single result (r IFG to r STN) is significant after correcting for multiple comparisons

(Bonferroni, new p threshold: 0.0083), in bold. The Chi Square and number of observations in the model are included.

Table 3

Association between microstructural integrity in inhibitory control networks and odds of falls in older adults.

Region	Odds	CI Low	CI High	p-Value	Chi Square Fit	n
rIFG - r STN	2.31	1.42	3.78	**0.00082**	0.000061	360
l preSMA - r STN	1.31	0.74	2.3	0.35	0.0098	200
l preSMA - l STN	1.23	0.76	2	0.41	0.0037	343
r preSMA - l STN	0.8	0.43	1.49	0.48	0.041	228
r preSMA - r STN	0.83	0.47	1.47	0.53	0.1	257
rIFG - l STN	1.06	0.61	1.86	0.83	0.0083	237

Table 3. Results of a logistic regression showing the association between the tractography of ROIs and the risk of falling in older people when accounting for physical activity. A result (r IFG to r STN) is significant after correcting for multiple comparisons (Bonferroni, new p threshold: 0.0083), the pis bold. The Chi Square and number of observation of the model are included.

Table 4

Association between microstructural integrity in inhibitory control networks and odds of falls in older adults.

Region	Odds	CI Low	CI High	p-Value	Chi Square Fit	n
rIFG (subregion 68) - r STN	3.59	1.7	7.56	**0.00079**	0.000027	221
rIFG (subregion 79) - r STN	2.08	1.06	4.05	0.032	0.007	249
rIFG (subregion 79) - l STN	1.79	0.84	3.8	0.13	0.16	130
rIFG (subregion 90) - r STN	0.58	0.28	1.19	0.14	0.21	186
rIFG (subregion 68) - l STN	1.22	0.45	3.31	0.7	0.0016	139
rIFG (subregion 90) - l STN	8.93E+21	0	-	1	0.0014	35

Table 4. Results of a logistic regression showing the association between the tractography of ROIs and the risk of falling in older people when accounting for physical activity. A result (r IFG to r STN) is significant after correcting for multiple comparisons (Bonferroni, new p threshold: 0.0083), the pis bold. The Chi Square and number of observation of the model are included.

Table 5

Prediction of fall risk in older adults by white matter microstructure.

Region	Odds	CI Low	CI High	P Value	Chi Square Fit	n
l preSMA - l STN	1.42	1.05	1.92	0.023	0.023	265
r preSMA - r STN	0.74	0.52	1.06	0.097	0.017	200
r preSMA - l STN	0.81	0.54	1.2	0.29	0.026	171
r IFG - r STN	1.04	0.78	1.39	0.776	0.125	276
r IFG - l STN	0.97	0.66	1.42	0.861	0.330	180
l preSMA - r STN	0.98	0.69	1.4	0.926	0.387	156

Table 5. Results of a logistic regression showing the prediction of the risk of falling in older adults using Apparent Fibre Density in pathways connecting targeted ROIs. No result is significant after correcting for

multiple comparisons (Bonferroni, new p threshold: 0.0083). The Chi Square and number of observation of the model are included.

Table 6

Association between microstructural integrity in inhibitory control networks and odds of falls in older adults

Region	Odds	CI Low	CI High	p-Value	Chi Square Fit	n
r preSMA - r STN	0.43	0.22	0.84	0.014	0.039	201
l preSMA - l STN	1.55	0.93	2.58	0.09	0.14	268
rIFG - r STN	1.16	0.74	1.84	0.52	0.28	282
rIFG - l STN	0.92	0.5	1.7	0.79	0.34	186
l preSMA - r STN	1.04	0.64	1.69	0.88	0.24	158
r preSMA - l STN	1.03	0.5	2.12	0.94	0.12	173

Table 6. Results of a logistic regression showing the prediction of the risk of falling in older adults using the Apparent Fibre Density. No result is significant after correcting for multiple comparisons (Bonferroni, new p threshold: 0.0083). The Chi Square and number of observation of the model are included.

Table 7

Association between microstructural integrity in inhibitory control networks and odds of falls in older adults.

Region	Odds	CI Low	CI High	p-Value	Chi Square Fit	n
r FFA - r STN	1.56	1.04	2.33	0.03	0.0227	178
lIFG - l STN	0.73	0.53	1	0.05	0.0001	282
lIFG - r STN	0.84	0.59	1.21	0.36	0.0042	197
l FFA - l STN	0.85	0.54	1.35	0.5	0.0050	124
r FFA - l STN	1.34	0.44	4.08	0.61	0.2286	39
l FFA - r STN	0.92	0.42	2	0.83	0.0192	70

Table 7. Results of a logistic regression showing the prediction of the risk of falling in older adults using the Apparent Fibre Density. No result is significant after correcting for multiple comparisons (Bonferroni, new p threshold: 0.0083). The Chi Square and number of observation of the model are included.

Table 8

Association between microstructural integrity in inhibitory control networks and odds of falls in older adults.

Region	Odds	CI Low	CI High	p-Value	Chi Square Fit	n
l IFG - l STN	1.38	1	1.91	0.05	0.0015	223
r FFA - l STN	0.34	0.09	1.3	0.12	0.1150	29
r FFA - r STN	1.37	0.89	2.09	0.15	0.0081	138
l FFA - r STN	1.42	0.73	2.78	0.3	0.2500	55
l FFA - l STN	0.99	0.54	1.84	0.98	0.1232	89
l IFG - r STN	1	0.65	1.53	1	0.1557	147

Table 8. Results of a logistic regression showing the prediction of the risk of falling in older adults using Apparent Fibre Density. No result is significant after correcting for multiple comparisons (Bonferroni, new p threshold: 0.0083). The Chi Square and number of observation of the model are included.

Figures

Figure 1

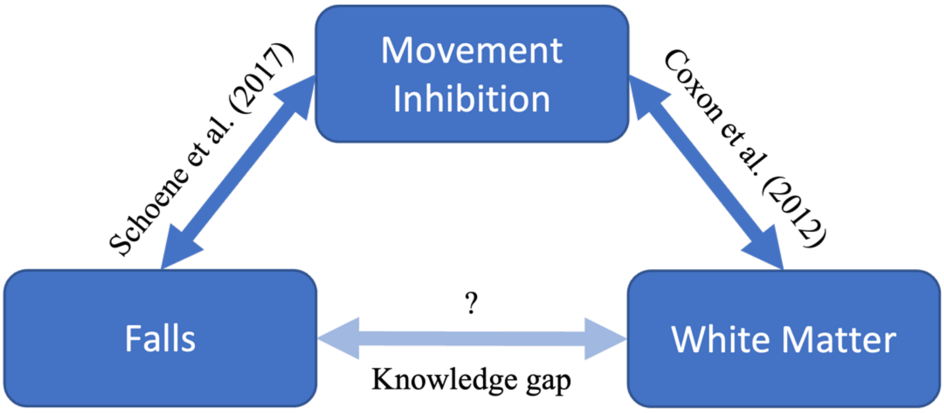

Figure 1. Theoretical framework. Schoene et al. (2017) have shown that improved performance on movement inhibition tasks are associated with a reduced number of falls in the real world. Coxon et al (2012) have shown that improved performance on movement inhibition tasks is associated with higher fractional anisotropy (FA) in right IFC and stronger connectivity between left preSMA and left STN, only in older adults. We therefore tested whether individuals who fall less may show stronger white matter microstructure in the regions identified as key nodes for inhibitory control.

Figure 2

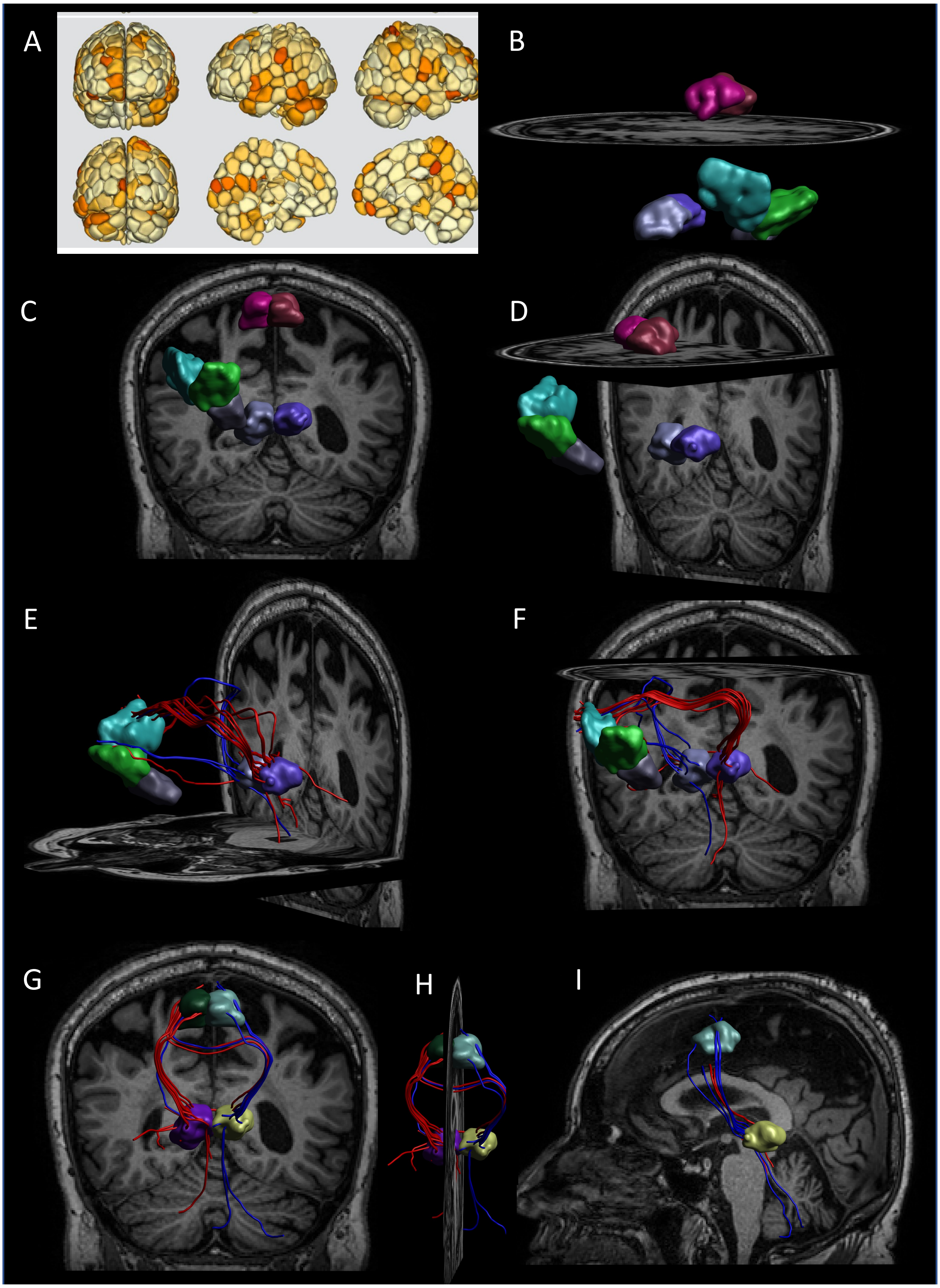

Figure 2. Regions of Interest and Reconstructed Streamlines. Panel A shows the Shen atlas parcellation that was used, with ROIs shown in Panels C-D selected for analysis. Panels E-F show different viewpoints of the ROIs with reconstructed streamlines passing between right and left STN and right IFG for one representative participant.

Panels G,H and I show different viewpoints of reconstructed streamlines passing between bilateral STN and preSMA.

Figure 3

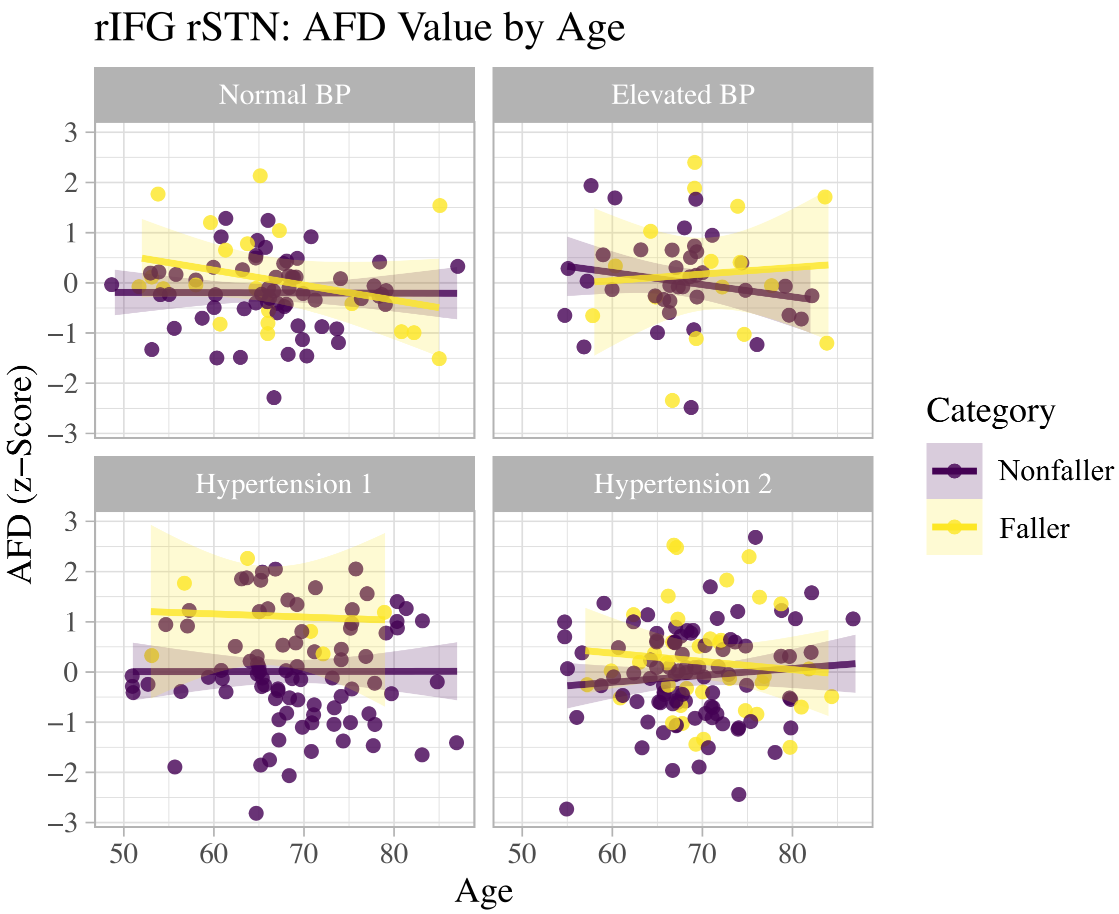

Figure 3. Figure 3 shows rIFG – rSTN fibre density (AFD) by Age, separated by Blood Pressure categories, with separate lines for fallers and nonfallers . There were significantly less fallers in the 'Hypertension 1' category. In the cohort with normal blood pressure, there are a total of 84 participants, 21 (25%) of which fell. For elevated blood pressure there are a total of 54 participants, 16 (29.63%) of which fell. For hypertension 1 there are a total of 93 participants, 6 (6.45%) of which fell. For hypertension 2 there are a total of 129 participants, 37 (28.68%) of which fell.

Figure 4

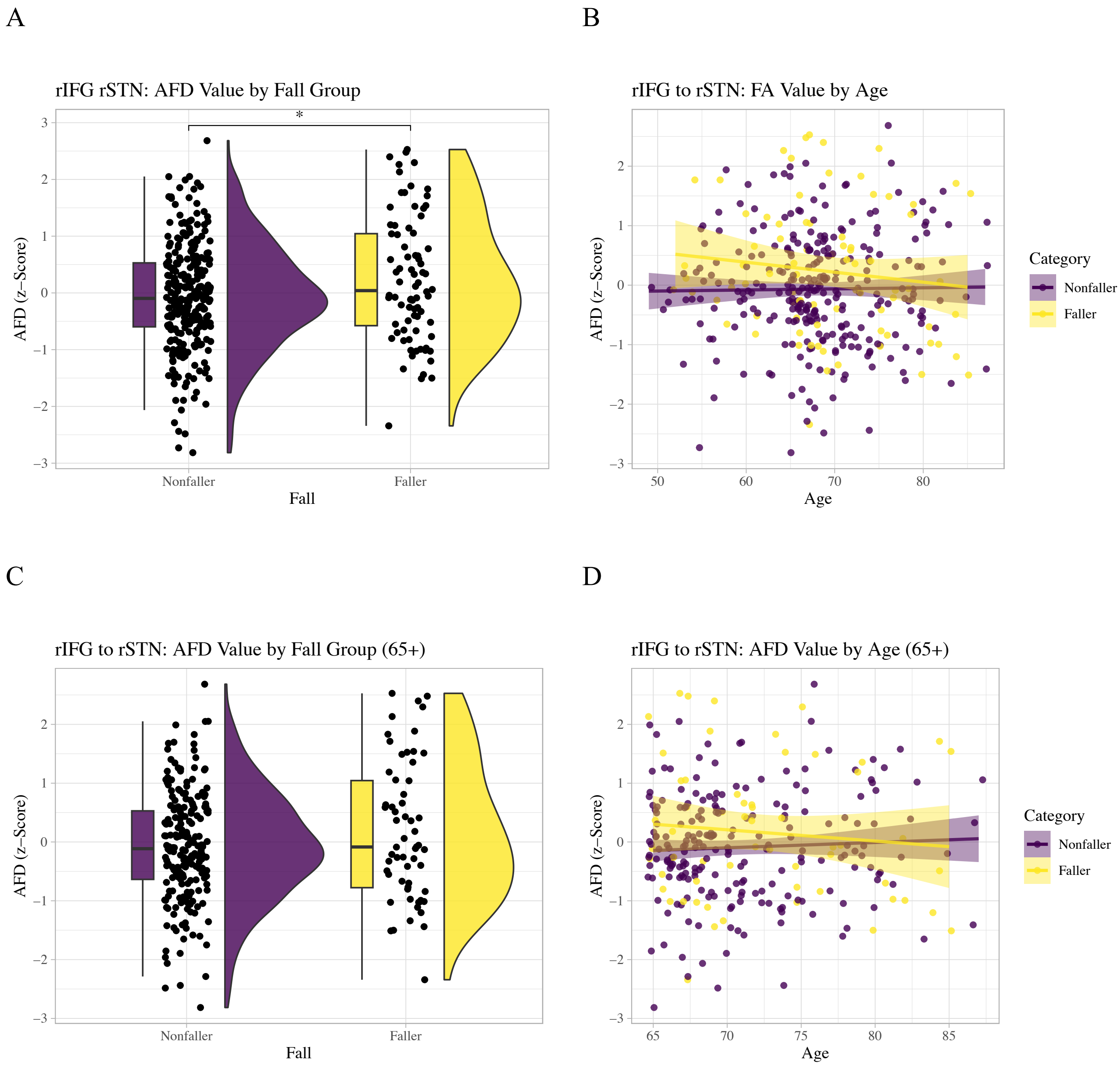

Figure 4. Figure A shows differences in the distribution of fallers vs nonfallers. Fallers seem to have overall higher AFD values. Figure B shows the difference in distribution according to age. Fallers also have a higher average AFD value, although this relationship is dependent on age. Figure C and D show the difference in distribution of fallers, but only including fallers of age 65 or more.

Figure 5

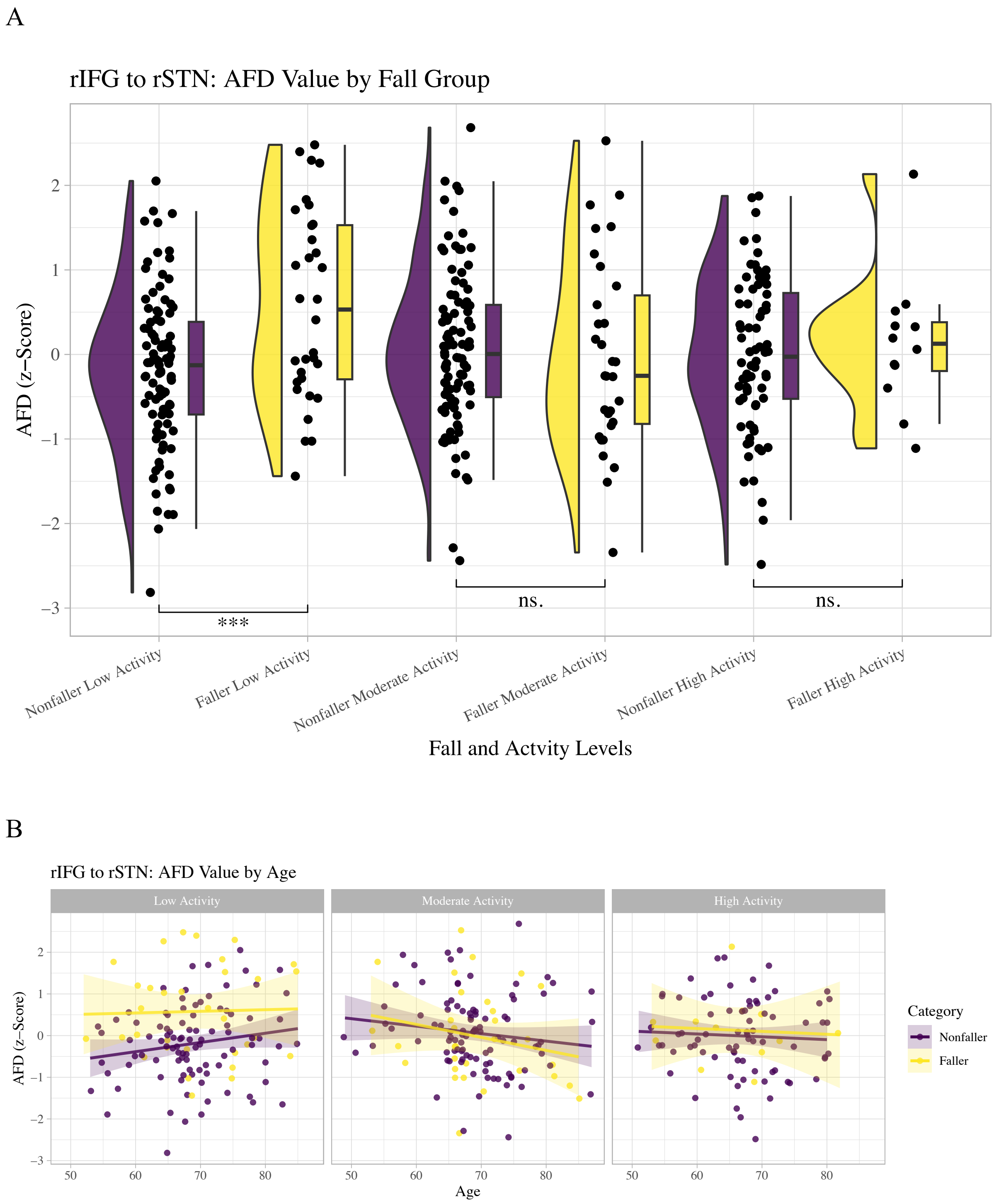

Figure 5. Panel A shows differences in the distribution of fallers vs nonfallers. Fallers have overall higher AFD values in the low activity condition, but not in high or moderate physical activity. Figure B shows the difference in distribution according to age. Fallers also have a higher average AFD value, and this relationship is less dependent on age when accounting for physical activity.

Graphical Abstract

White matter fibre density in the brain's inhibitory control network is associated with falling in older adults

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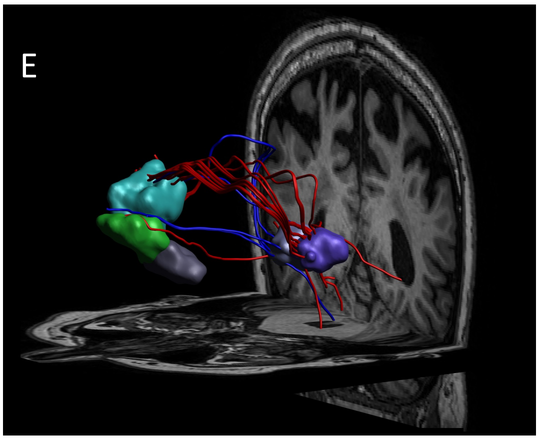
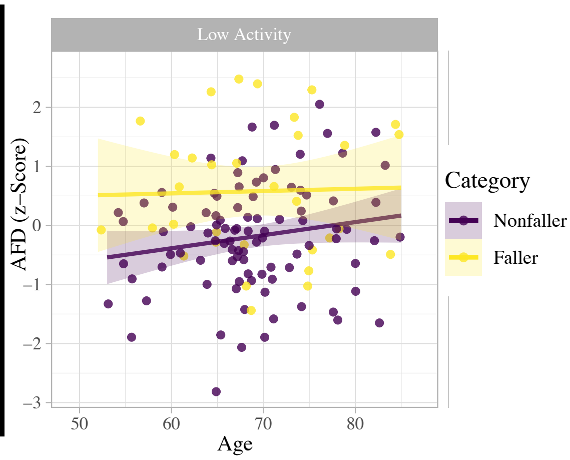
Recent research has indicated that the relationship between age-related cognitive decline and falling may be mediated by the individual's capacity to quickly cancel or inhibit a motor response. This longitudinal investigation demonstrates that higher white matter fibre density in the motor inhibition network paired with low physical activity was associated with falling in older adults.





Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

CRediT Contributions

Conceptualization: K.R. and D.B.; Data curation: S.K.; Formal analysis: C.S.; Funding acquisition: K.R.; R.A.K, Methodology: C.S., K.R. and D.B.; Project administration: R.A.K, C.S. and K.R.; Resources: S.K.; Software: C.S.; Supervision: K.R.; Visualization: C.S.; Writing – original draft: C.S.; Writing - review & editing: C.S., K.R., D.B., J.M., R.A.K., V.A.S., C.D. and S.K.

Ethical Statement

Ethical approval for the TILDA study was obtained from the Faculty of Health Sciences Research Ethics Committee the Trinity College Dublin Research Ethics Committee. Signed informed consent was obtained from all respondents prior to participation. Additional ethics approval was received for the MRI sub-study from the St James's Hospital/Adelaide and Meath Hospital, Inc. National Children's Hospital, Tallaght (SJH/AMNCH) Research Ethic Committee, Dublin, Ireland.

Data Availability Statement

The datasets generated during and/or analysed during the current study are not publicly available due to data protection regulations but are accessible at TILDA on reasonable request. The procedures to gain access to TILDA data are specified at https://tilda.tcd.ie/data/accessing-data/, (accessed on 29th November 2023).