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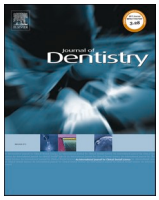

Tooth loss and regional grey matter volume

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ABSTRACT

Objectives: To investigate whether tooth loss was associated with regional grey matter volume (GMV) in a group of community dwelling older men and women from Ireland.
Methods: A group of 380 dementia-free men and women underwent a dental examination and had a Magnetic Resonance Imaging (MRI) scan as part of The Irish Longitudinal Study of Aging (TILDA). Cortical parcellation was conducted using Freesurfer utilities to produce volumetric measures of gyral based regions of interest. Analysis included multiple linear regression to investigate the association between tooth loss and regional GMVs with adjustment for various confounders.
Results: The mean age of participants was 68.1 years (SD 7.3) and 51.6% of the group were female. 50 (13.2%) of the participants were edentulous, 148 (38.9%) had 1-19 teeth, and 182 (47.9%) had ≥20 teeth. Multiple liner regression analysis with adjustment for a range of potential confounders showed associations between the number of teeth and GMVs in the paracentral lobule and the cuneus cortex. In the paracentral lobule, comparing participants with 1-19 teeth versus edentates there was an increase in GMV of β=323.0mm^3 (95% Confidence Interval [CI] 84.5, 561.6) and when comparing participants with ≥20 teeth to edentates there was an increase of β=382.3mm^3 (95% CI 126.9, 637.7). In the cuneus cortex, comparing participants with ≥20 teeth to edentates there was an increase in GMV of β=380.5mm^3 (95% CI 69.4, 691.5).
Conclusions: In this group of older men and women from Ireland, the number of teeth was associated with GMVs in the paracentral lobule and the cuneus cortex independent of various known confounders.
Clinical significance: Although not proof of causation, the finding that tooth loss was associated with regional reduced GMV in the brain may represent a potential explanatory link to the observed association between tooth loss and cognitive decline.

1. Introduction

Tooth loss is a common oral condition that leads to functional, aesthetic, and social problems that have been shown to affect quality of life and self-esteem [1,2]. Total tooth loss (edentulism) is a particularly debilitating and challenging condition. The Global Burden of Disease (2015) study identified that edentulism was responsible for causing 7.6 million DALYs (disability-adjusted life years) [3]. Although global edentulism levels have decreased in recent decades, prevalence remains high amongst older individuals [4].

In addition to the local effects of tooth loss, evidence from several epidemiological studies have suggested an association between tooth loss and cognitive decline [5–7]. A recent meta-analysis reported that individuals with <20 teeth were at a higher risk than those with ≥20 teeth for developing both cognitive decline with a Hazard Ratio [HR] of 1.26 (95% Confidence Interval [CI] = 1.14 to 1.40) and dementia with a HR of 1.22 (95% CI = 1.04 to 1.43) [8]. It is estimated that that the number of people living with dementia will increase from 57.4 (95% uncertainty interval 50.4–65.1) million cases in 2019 to 152.8 (130.8–175.9) million cases in 2050 [9]. Therefore, the identification of potentially modifiable risk factors in the aetiology and progression of cognitive decline / dementia is important [6].

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There are several proposed mechanisms which may explain the observed association between tooth loss and cognitive decline [10]. One such mechanism is the concept that tooth loss may negatively impact the somatosensory feedback system to the brain, particularly during mastication [11]. Neuroimaging studies in humans utilising functional magnetic resonance imaging (MRI) have found increased activity in cortical sensory and motor regions, the subcortical regions, and the cerebellum during chewing [12–15]. The neurophysiological consequences of tooth loss are disruption or loss of this somatosensory feedback (including nociceptive and proprioceptive) from teeth and the surrounding periodontal ligament [16]. In animal models, it has been demonstrated that tooth loss induces regional grey matter volume (GMV) changes in the brain [17,18]. It is unknown how these changes occur but it may reflect structural changes in glia, neurons, and blood vessels that result from changes in their number, function and volume [19]. Cross-sectional and longitudinal studies have demonstrated clear relationships between cognitive decline and the atrophy of specific brain regions [20]. Therefore, regional GMV changes related to tooth loss may represent a potential cause-effect relationship between tooth loss and cognitive decline.

Despite biological plausibility, there have only been a limited number of studies conducted in humans investigating the effect of tooth loss and GMV change. The majority of these have focussed on tooth loss and *total* GMV change. Of note, Egashira and co-workers (2021) reported that in a group if 15 participants with cognitive decline, the number of teeth was correlated with whole brain atrophy derived from voxel based analysis of MRI [21]. In a larger study of 394 participants, Dintica and colleagues (2018) found that self-reported tooth loss and edentulism were associated with a lower total GMV [22]. In a recent study conducted by Matsuyama and colleagues (2022), total GMV was reported to mediate the relationship between self-reported number of teeth and cognitive function in a group of 494 Japanese older adults [23].

Comparatively fewer studies have focused on tooth loss and *regional* GMV change. In a study of 24 participants, Kobayashi and colleagues (2018) found that older edentulous subjects showed a reduction in GMV in the right hippocampus, caudate nucleus and temporal pole [24]. In a case-control study of 70 participants (40 cases, 30 controls), Lin and co-workers (2020) found that tooth loss may be preferentially related to structural differences in the medial temporal lobe in cognitively impaired older adults [25]. Given the fewer number and size of such studies, the aim of the current study was to investigate whether tooth loss was associated with regional GMV in a group of dementia free, community dwelling older men and women from Ireland. We hypothesised that tooth loss may be associated with GMV in regions of the brain that are associated with somatosensory feedback function during mastication.

2. Methodology

2.1. Population

Subjects were recruited from the Irish Longitudinal Study of Ageing (TILDA), which is a nationally representative, large prospective cohort study on the social, economic, and health circumstances of community-dwelling adults aged 50 years and older in Ireland. TILDA uses a multistage stratified clustered sampling strategy using the Geodirectory, which is a list of all the residential addresses in the Republic of Ireland, as the sampling frame. The target sample consisted of a nationally representative sample of individuals living in private households aged 50 and over in Ireland. Details of TILDA's design including survey methodology and weighting scheme have previously been published [26,27]. Data on a broad range of domains including health status, healthcare utilisation, demographic, social and economic circumstances are all collected at successive 'waves' performed biennially. At Wave 3 (2014-15), 4307 participants attended for an in-person comprehensive health assessment at the TILDA health centre, Trinity College Dublin. Alongside the comprehensive health assessments, subjects were offered an optional oral health assessment of which 2508 participants took part [5,28].

Additionally, a group of participants that completed the Wave 3 health assessments were also invited to take part in a MRI sub-study [29]. In total, 578 participants attended for scanning; 18 did not provide data (due to claustrophobia/anxiety [n = 14] or MRI contraindication [n = 4]); 61 scans were excluded due to data quality and processing errors (motion artifacts [n = 33], gray matter/white matter lesions [n = 18], image shearing of the cerebellum [n = 2], or technical error [n = 8]). MRIs were performed at the National Centre for Advanced Medical Imaging, Dublin, Ireland. The mean (SD) delay between the oral health assessment and MRI examination was 62 (40) days. The current study is based on a cross sectional analysis of 380 subjects that completed both the oral health assessments and participated in the MRI sub-study at Wave 3 (**Fig. 1**).

Ethical approval for TILDA was obtained from the Research Ethics Committee of the Faculty of Health Sciences, Trinity College Dublin. Participation was voluntary and all participants provided informed, written consent. Additional ethical approval was received for the MRI sub-study from the St James's Hospital/Adelaide and Meath Hospital, Incorporating the National Children's Hospital, Tallaght Research Ethic Committee, Dublin, Ireland. Those attending for MRI were also required to complete an additional MRI-specific consent form. Individuals were not eligible for inclusion if they reported a doctor's diagnosis of dementia. Furthermore, individuals who were not able to consent personally because of severe cognitive impairment (at interviewer's discretion) were also excluded.

2.2. Oral health assessment

The oral health assessment was based on World Health Organization (WHO) epidemiological survey methodology [30]. All oral health assessments were completed by one of four trained dentists who had been calibrated against a "gold standard" set by a senior clinical researcher prior to the study commencing. Regular meetings took place throughout the duration of the study to ensure inter- and intra-examiner consistency and reproducibility.

Tooth presence was recorded for each of the 32 teeth to calculate the number of natural teeth present in each adult. The examiners used clinical judgement regarding tooth morphology and took into account the respondent's previous dental history if doubt existed as to the correct notation for a particular missing tooth. Participants were categorised based upon the number of natural teeth into three groups (≥20 teeth; 1-19 teeth; and Edentulous). The number of natural teeth as a continuous variable (0 to 32) was also used as an additional exposure variable.

2.3. MRI protocol and T1-weighted acquisition

Scans were acquired at the National Centre for Advanced Medical Imaging (CAMI), St. James' Hospital, Dublin, via a 3T system (Achieva, Philips Medical Systems, The Netherlands) with 32-channel head coil. The protocol included a variety of scans, including a T1-weighted MRI acquired using a 3D Magnetisation-Prepared Rapid Gradient Echo (MP-RAGE) sequence, with the following parameters: FOV (mm): 240 × 218 × 162; voxel size (mm): 0.8 × 0.8 × 0.9; SENSE factor: 2; TR: 6.7ms; TE: 3.1ms; flip angle: 8°.

2.4. Data inspection and volumetric measures

Brain images were parcellated using the Desikan Killiany atlas, with 34 cortical regions of interest (ROIs) per hemisphere [31]. We selected the Desikan-Killiany atlas owing to its well-validated implementation within FreeSurfer. FreeSurfer utilities implement a technique for automatically assigning a neuroanatomical label to each location on a cortical surface model based on probabilistic information estimated

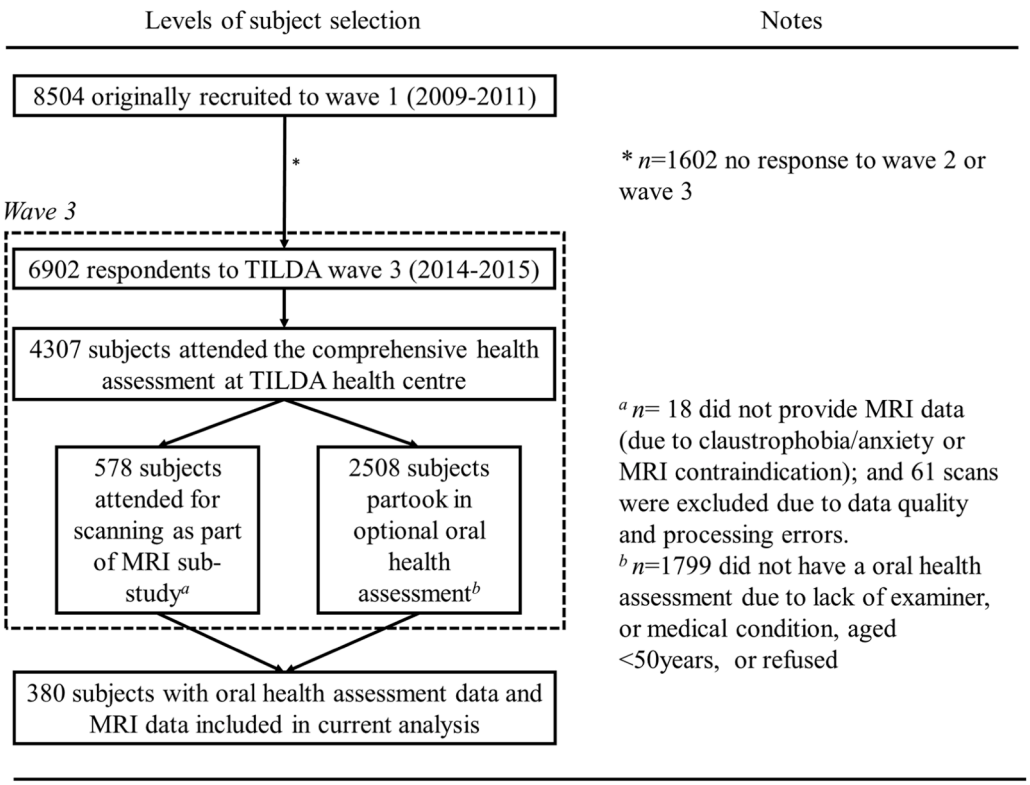

Fig. 1. Recruitment and enrolment of study participants.

from a manually labelled training set. This procedure incorporates both geometric information derived from the cortical model, and neuroanatomical convention. The result is a complete labelling of cortical sulci and gyri. Right and left volumes were summed for each participant to obtain total ROI volumes in cubic millimetres (mm^3). Estimated total intracranial volume (eTIV) was calculated using the FreeSurfer recon-all processing pipeline, and overall GMV was also extracted. Based on previous evidence [11,13,15,32-37], we pre-selected 10 potential brain ROIs that have been associated with somatosensory feedback particularly during mastication. ROIs included: superior frontal gyrus; middle frontal gyrus; anterior cingulate; insula; superior parietal cortex; precentral gyrus; paracentral lobule; postcentral gyrus; cuneus cortex; and hippocampus.

2.5. Covariates

Covariates of theoretical, practical or previous empirical evidence of association with tooth loss or GMV change were included. Age (years) was used as a continuous variable in the statistical modelling. Sex as male / female. Education was classified as: primary (some primary / not complete; primary or equivalent); secondary (intermediate / junior / group certificate or equivalent; leaving certificate or equivalent); and tertiary (diploma / certificate; primary degree; postgraduate / higher degree). Marital status was categorised into 4 categories: married; living alone; separated / divorced; and widowed. Body weight and height were measured using standard procedures during the health assessment. BMI was calculated as weight/height^2 (kg/m^2). Smoking behaviour was divided into three categories: never smoked, former smoker and current smoker. Problematic alcohol intake was measured as a score of $\geq$2 on the Cut, Annoyed, Guilty, Eye-opener (CAGE) questionnaire [38]. Exercise level was measured with the International Physical Activity Questionnaire short form [39], and is represented as a three-level variable: low, moderate, and high. Co-morbidity variables included a doctor's previous diagnosis of atherosclerotic cardiovascular disease (yes/no), stroke or transient ischemic attack (yes/no), high blood pressure (yes/no), and diabetes (yes/no). Socio-Economic Status (SES) was derived based on respondent's current occupation (or historic occupation—defined as the job title of the highest paying job they ever held—if they had retired). The coding of occupations followed the Irish Central Statistics Office social class schema: professional; managerial; non-manual; skilled manual; semi-skilled; unskilled; and all others gainfully occupied but unknown. These were then aggregated into 3 categories. Symptoms of depression were assessed using the Centre for Epidemiological Studies Depression Scale (CESD) [40], and dichotomised based on a cut off CESD $\geq$9. All covariate data utilised relates to data collected at Wave 3 (the time of the oral health assessment and MRI acquisition).

2.6. Statistical analysis

Comparisons of baseline characteristics of the study sample were made based on dentate status (Edentate; 1-19 teeth; $\geq$20 teeth). Analysis of variance (ANOVA) was utilised to compare continuous variables, and chi-square test for categorical variables. To estimate selection bias, the study sample (n=380) was also compared to the rest of the Wave 3 cohort excluded from the analysis (n=6307), **(Supplementary Information, Table S1)**. Unadjusted regional GMV data by dentate status was presented using Boxplots and compared using ANOVA with post hoc Bonferroni testing.

Multiple linear regression analysis was then performed to investigate the association between dentate status (Edentate; 1-19 teeth; $\geq$20 teeth) and regional GMV (mm^3). Models were fitted to adjust for potential confounding variables. A 'basic model' included adjustment for age, sex, education and head size; followed by a 'fully adjusted model' with additional adjustment for BMI, exercise, smoking, alcohol, atherosclerotic cardiovascular disease (ACVD), stroke, hypertension, diabetes, SES, marital status, and depression. A test for trend was performed across dentate status categories. The same modelling was carried out for each of the ten brain ROI. Multiple linear regression analysis was also repeated using the number of teeth in continuous form (per tooth

increase) as an additional exposure variable.

The level of statistical significance was set at $p<0.05$. Analyses were performed using Stata 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.).

3. Results

The mean age of participants was 68.1 years (SD 7.3) and 51.6% of the group were female. 50 (13.2%) of the participants were edentulous, 148 (38.9%) had 1-19 teeth, and 182 (47.9%) had ≥20 teeth. General characteristics of the study sample (n=380), compared to those excluded from the analyses (n=6307) are shown in **Supplemental Information, Table S1**. Subjects that were included in the current analysis were marginally older (68.1 versus 66.6 years); were less likely to be smokers; had a higher educational achievement; and had a higher SES background. In terms of comorbidities (ACVD, stroke, diabetes & hypertension) and other risk factors there were no differences between those included in the current analysis and those excluded.

Characteristics of participants by dentate status are reported in Table 1. Edentulous participants had a mean age of 72.9 years (SD 6.6), those with 1-19 teeth had a mean age of 69.7 years (SD 6.0), and those with ≥20 teeth had a mean age of 65.5 years (SD 7.5). There was a difference across smoking categories with greater proportions of current and former smokers in those that had experienced more tooth loss (both edentulous and those with 1-19 teeth). There was a difference in the presence of diabetes across dentate categories with 18% in edentulous participants, 8.1% in those with 1-19 teeth, and 5.5% in those with ≥20 teeth. Highest educational achievement was different across dentate categories with 55% of participants reaching third level or higher in the ≥20 teeth group, compared to 32.4% in the 1-19 teeth group, and 20.0% in the edentulous group. Similarly, social class structure was different with a higher proportions of managerial / technical / professional occupations in the ≥20 teeth group at 47.8%, 37.8% in the 1-19 teeth group, and 22.0% in the edentulous group. Total GMVs were also different across dentate categories with means of 565.7cm^3 (SD 44.6) in edentate subjects, 580.5 cm^3 (SD 50.6) in those with 1-19 teeth, and 592.1 cm^3 (SD 49.1) in those with ≥20 teeth.

Regional GMV data by dentate status are depicted in Fig. 2, and additionally described in **Supplemental Information, Table S2**. There were differences across dentate categories in the anterior cingulate, the superior parietal cortex, the precentral gyrus, the paracentral lobule, the cuneus cortex, and the hippocampus. Post-hoc Bonferroni analysis showed that all these regions had smaller GMVs in edentulous participants compared to those with ≥20 teeth.

Multiple linear regression was used to investigate the association between dentate status (Edentate; 1-19 teeth; ≥20 teeth) and regional GMV (mm^3), Table 2. With basic adjustment for age, sex, education, and head size, associations across dentate categories and GMV were observed in the superior parietal cortex (≥20 teeth versus Edentate), the precentral gyrus (≥20 teeth versus Edentate), the paracentral lobule (1-19 teeth versus Edentate, and ≥20 teeth versus Edentate), and the cuneus cortex (1-19 teeth versus Edentate, and ≥20 teeth versus Edentate). Fully adjusted models showed associations across dentate categories and GMVs in the anterior cingulate (≥20 teeth versus Edentate), the paracentral lobule (1-19 teeth versus Edentate, and ≥20 teeth versus Edentate), and the cuneus cortex (≥20 teeth versus Edentate). Positive tests for trend across dentate categories were also observed for these three brain ROIs.

Utilising the number of teeth as a continuous variable (Table 3), associations between the number of teeth (per tooth increase) and regional GMV (mm^3) were found in the superior parietal cortex (β=35.5, 95% CI 3.4-67.6), the paracentral lobule (β=12.4, 95% CI 3.1-21.7) and the cuneus cortex (β=15.0, 95% CI 3.7-26.2), in the fully adjusted models.

Table 1
Characteristics of participants by dentate status, n = 380.

	Edentulous n=50	1-19 teeth n=148	≥20 teeth n=182	p	
Age, mean (SD)	72.9 (6.6)	69.7 (6.0)	65.5 (7.5)	**<0.001**	
Sex, female, *n (%)*	30 (60.0%)	74 (50.0%)	92 (50.6%)	0.44	
BMI, mean (SD)	26.2 (6.0)	26.1 (5.8)	25.7 (6.4)	0.73	
Exercise levels (IPAQ), *n* (%)					
Low	23 (46.9%)	51 (36.7%)	61 (34.7%)	0.29	
Moderate	18 (36.7%)	48 (34.5%)	73 (41.5%)		
High	8 (16.3%)	40 (28.8%)	42 (23.9%)		
Smoking, *n* (%)					
Never	20 (40.0%)	70 (47.3%)	112 (61.5%)	**0.02**	
Former	24 (48.0%)	66 (44.6%)	62 (34.1%)		
Current	6 (12.0%)	12 (8.11%)	8 (4.4%)		
Problem drinking (Cage ≥2), *n* (%)	3 (6.0%)	11 (7.4%)	18 (9.9%)	0.75	
ACVD, *n* (%)	5 (10.0%)	11 (7.4%)	6 (3.3%)	0.11	
Stroke, *n* (%)	1 (2.0%)	0 (0.0%)	2 (1.1%)	0.31	
Diabetes, *n* (%)	9 (18.0%)	12 (8.1%)	10 (5.5%)	**0.02**	
Hypertension, *n* (%)	23 (46.0%)	53 (35.8%)	55 (30.2%)	0.10	
SES, *n* (%)					
Routine, manual, other	23 (46.0%)	56 (37.8%)	40 (22.0%)	**<0.01**	
Intermediate	16 (32.0%)	36 (24.3%)	55 (30.2%)		
Managerial, technical	11 (22.0%)	56 (37.8%)	87 (47.8%)		
Highest educational achievement, *n* (%)					
Primary / none	22 (44.0%)	42 (28.4%)	22 (12.1%)	**<0.001**	
Secondary	18 (36.0%)	58 (39.1%)	60 (33.0%)		
Third / higher	10 (20.0%)	48 (32.4%)	100 (55.0%)		
Marital status, *n* (%)					
Married	36 (72%)	113 (76.4%)	137 (75.3%)	0.35	
Never married	4 (8%)	9 (6.1%)	14 (7.7%)		
Sep / divorced	0 (0.0%)	9 (6.1%)	12 (6.6%)		
Widowed	10 (20.0%)	17 (11.5%)	19 (10.4%)		
Depression (CESD ≥9), n (%)	6 (12.0%)	10 (6.8%)	18 (10.0%)	0.44	
Total Grey Matter Volume, mm^3, mean (SD)	565684.8 (44597.4)	580491.8 (50617.4)	592061.5 (49097.6)	**<0.01**	

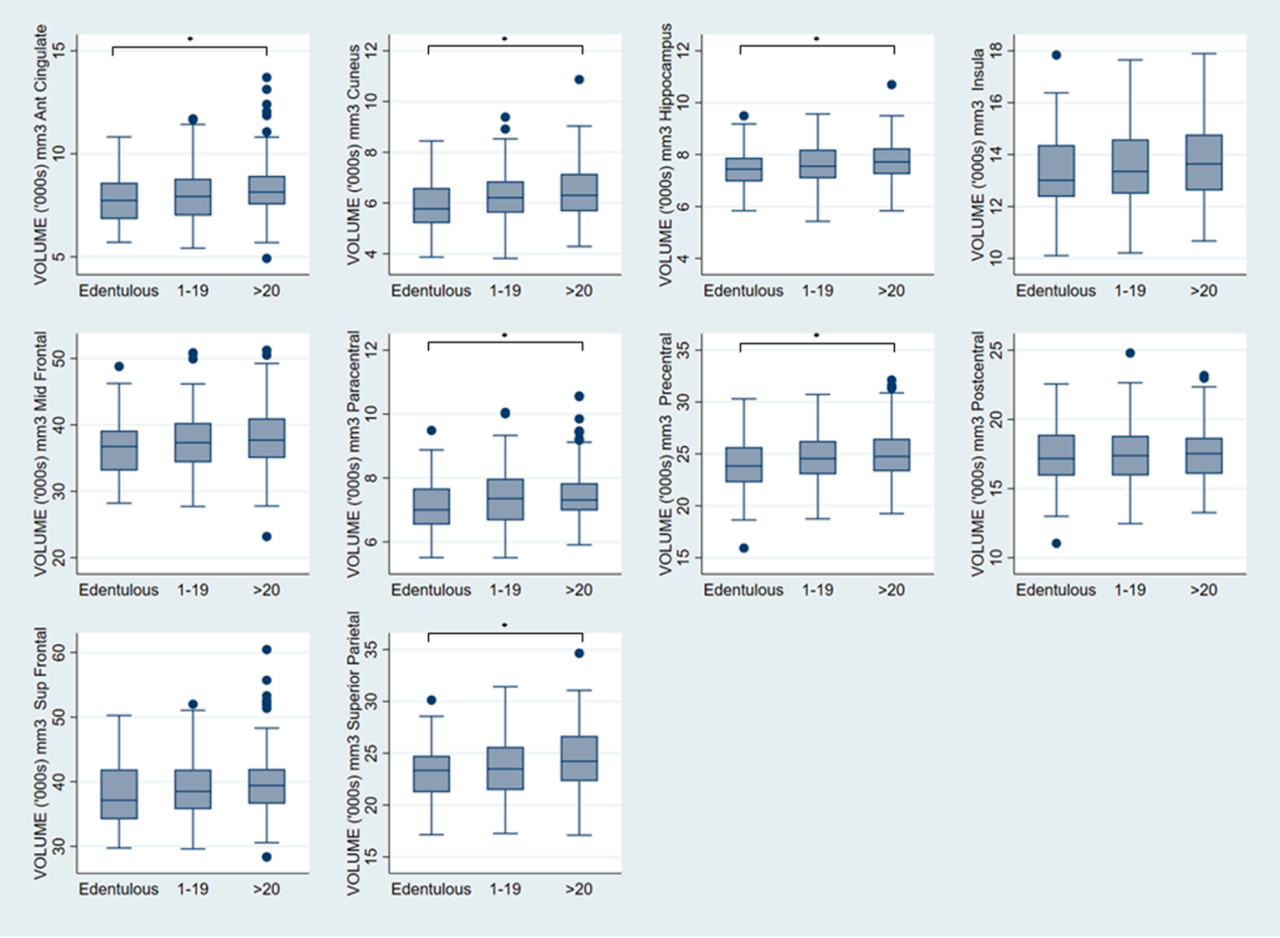

Fig. 2. Box plot summaries of regional Grey Matter Volume by dentate status, n=380. * p<0.05 (ANOVA-post hoc test Bonferroni).

Table 2
Summary table of multiple linear regression analyses investigating association of dentate status (Edentate; 1-19 teeth; ≥20 teeth) with various brain regions of interest adjusted for various confounders, n=380.

Region of interest (dependent variables)	Tooth category (ref. Edentate group)	Basic model β (95% CI)	*p* for trend	Fully adjusted model β (95% CI)	*p* for trend
Superior frontal gyrus	1-19 teeth	867.2 (-337.5, 2071.9)	0.22	899.3 (-326.7, 2125.3)	0.33
	≥20 teeth	946.6 (-320.9, 2214.2)		866.9 (-445.8, 2179.5)	
Middle frontal gyrus	1-19 teeth	799.8 (-310.9, 1910.5)	0.10	811.6 (-325.9, 1949.1)	0.10
	≥20 teeth	1056.9 (-111.7, 2225.6)		1109.4 (-108.5, 2327.3)	
Anterior cingulate	1-19 teeth	291.2 (-78.3, 660.7)	0.07	277.2 (-98.2, 652.7)	**0.03**
	≥20 teeth	386.0 (-2.8, 774.7)		**439.8 (37.8, 841.9)**	
Insula	1-19 teeth	219.0 (-145.1, 583.0)	0.24	229.2 (-148.8, 607.2)	0.29
	≥20 teeth	303.5 (-79.5, 686.5)		259.6 (-145.1, 664.4)	
Superior parietal cortex	1-19 teeth	564.0 (-243.6, 1371.5)	0.04	611.8 (-214.6, 1438.2)	0.06
	≥20 teeth	908.8 (59.2, 1758.5)		883.4 (-1.4, 1768.2)	
Precentral gyrus	1-19 teeth	650.2 (-18.5, 1318.9)	0.04	554.7 (-131.9, 1241.3)	0.12
	≥20 teeth	813.2 (109.6, 1516.8)		671.1 (-64.0, 1406.3)	
Paracentral lobule	1-19 teeth	288.7 (52.1, 525.3)	0.02	**323.0 (84.5, 561.6)**	**0.01**
	≥20 teeth	348.3 (99.3, 597.2)		**382.3 (126.9, 637.7)**	
Postcentral gyrus	1-19 teeth	170.0 (-368.7, 708.7)	0.59	185.6 (-361.8, 732.9)	0.41
	≥20 teeth	-41.9 (-608.7, 524.8)		-105.2 (-691.2, 480.8)	
Cuneus cortex	1-19 teeth	286.6 (2.4, 570.8)	0.04	246.1 (-44.5, 536.6)	**0.02**
	≥20 teeth	354.0 (55.0, 653.0)		**380.5 (69.4, 691.5)**	
Hippocampus	1-19 teeth	-8.8 (-221.5, 203.9)	0.58	-24.4 (-244.3, 195.5)	0.41
	≥20 teeth	-49.9 (-273.7, 173.9)		-83.4 (-318.8, 152.1)	

Notes.
Regression coefficients (β) represent regional change in grey matter volume (mm^3) in either the 1-19 teeth category or ≥20 teeth category, versus the edentulous group (reference group).
Basic model = adjusted for age, sex, education, head size.
Fully adjusted model = adjusted for age, sex, education, head size, bmi, exercise, smoking, alcohol, ACVD, Stroke, hypertension, diabetes, SES, Marital Status, Depression.
Values in **bold** represent p<0.05 in the fully adjusted model.

Table 3
Summary table of multiple linear regression analyses investigating association of number of teeth (continuous variable) with various brain region of interest adjusted for various confounders, n=380.

Region of interest (dependent variables)	Basic model β (95% CI)	*p*	Fully adjusted model β (95% CI)	*p*
Superior frontal gyrus	38.6 (-6.9, 84.0)	0.10	37.5 (-10.2, 85.1)	0.12
Middle frontal gyrus	31.2 (-10.8, 73.2)	0.15	35.1 (-9.2, 79.4)	0.12
Anterior cingulate	7.6 (-6.4, 21.6)	0.29	11.2 (-3.4, 25.8)	0.13
Insula	11.4 (-2.4, 25.1)	0.11	9.3 (-5.4, 24.0)	0.21
Superior parietal cortex	36.8 (6.4, 67.3)	0.02	**35.5 (3.4, 67.6)**	**0.03**
Precentral gyrus	26.7 (1.4, 51.9)	0.04	20.9 (-5.8, 47.6)	0.13
Paracentral lobule	10.5 (1.6, 19.5)	0.02	**12.4 (3.1, 21.7)**	**<0.01**
Postcentral gyrus	-3.5 (-23.9, 16.8)	0.73	-7.4 (-28.7, 13.9)	0.50
Cuneus cortex	13.2 (2.5, 23.9)	0.02	**15.0 (3.7, 26.2)**	**<0.01**
Hippocampus	-0.3 (-8.3, 7.8)	0.95	-1.7 (-10.3, 6.8)	0.69

Notes.
Regression coefficients (β) represent regional change in grey matter volume per tooth increase (mm^3/tooth increase).
Basic model = adjusted for age, sex, education, head size
Fully adjusted model = adjusted for age, sex, education, head size, bmi, exercise, smoking, alcohol, ACVD, Stroke, hypertension, diabetes, SES, Marital Status, depression
Values in **bold** represent $p<0.05$ in the fully adjusted model.

4. Discussion

The main finding of this cross-sectional study was that in a group of older men and women from Ireland, the number of teeth was associated with regional GMVs in the paracentral lobule and cuneus cortex. This finding was consistent whether analysis was performed utilising dentate status (categorical variable) or number of teeth (continuous variable) as the main exposure variables. In the paracentral lobule, comparing participants with 1-19 teeth versus edentates there was an increase in GMV of β=323.0mm^3 (95% CI 84.5, 561.6) and when comparing participants with ≥20 teeth to edentates there was an increase of β=382.3mm^3 (95% CI 126.9, 637.7), whilst controlling for other potential confounding variables. In the cuneus cortex, comparing participants with ≥20 teeth to edentates there was an increase in GMV of β=380.5mm^3 (95% CI 69.4, 691.5). Per tooth increase there was an increase in GMV in the paracentral lobule of β=12.4mm^3 (95% CI 3.1-21.7) and in the cuneus cortex of β=15.0mm^3 (95% CI 3.7-26.2).

Neuroimaging studies of the sensorimotor areas S1/M1 of the brain, including the precentral gyrus, paracentral lobule, and post central gyrus, have consistently shown increased activation during a chewing task [12,13,15,32,41]. The paracentral lobule is on the medial surface of the cerebral hemisphere and is the continuation of the precentral and postcentral gyri, and has both motor and sensory innervations. Our finding that the number of teeth was associated with GMV in the paracentral lobule, may support a hypothesis that tooth loss might directly impact somatosensory feedback to this region of the brain resulting in smaller GMV. Of course, in a cross-sectional study we are unable to determine if the tooth loss was the *cause* of reduced GMV or merely *associated* with it [42]. However, previous animal studies have found that in a controlled setting the removal of teeth in mice lead to GMV decreases in both the S1 and M1 cortices [17]. Our finding of an association between the number of teeth and GMV in the cuneus cortex may potentially represent an indirect effect of tooth loss. Rather than a direct site for somatosensory feedback, motor cortical seeds have been shown to have functional connections with the cuneus cortex [15]. Therefore, the observed association between the number of teeth and GMV change in the cuneus cortex may represent an indirect consequence of loss of functional connectivity. Alternatively, the cuneus cortex has also been implicated in changes associated with the trigeminal nerve in trigeminal neuralgia [34], or more generally with processing swallowing and tongue movement [43]. Whether tooth loss and associated somatosensory feedback alteration may impact either of these mechanisms is unknown.

Other regions appeared to be more dependent on which exposure variable was used, and therefore should be interpreted with caution. When performing analysis using dentate status (categorical variable) as the exposure variable an additional association was observed in the anterior cingulate area when comparing ≥20 teeth versus edentate, β=439.8mm^3 (95% CI 37.8, 841.9). In an animal study Xu and coworkers (2015) found that tooth loss led to higher-order cognitive deficits accompanied by a weakening in the connection between the anterior cingulate area and amygdala [44]. When performing analysis using number of teeth (continuous variable) as the exposure variable an additional association was found with the superior parietal cortex. Per tooth increase there was an increase in GMV of β=35.5mm^3 (95% CI 3.4, 67.6). In older persons the superior parietal cortex has been found to be one of the main mastication related hubs outside of the S1/M1 region [35]. The observed association between the number of teeth and GMV change in the superior parietal cortex may represent an indirect consequence of loss of functional connectivity to this region.

No associations were observed for the superior frontal gyrus, middle frontal gyrus, insula, precentral gyrus, postcentral gyrus, and hippocampus. These regions were included in our analysis based on previous evidence for these regions associating with mastication [11,13,15,32-37]. However, evidence for brain regions associating with mastication is mainly based on functional MRI studies showing increased brain activity in a specific region during a chewing task. Therefore, our finding that tooth loss in these regions did not associate with a static GMV change should not be interpreted that there is no impact of loss of teeth. Further studies investigating tooth loss where participants perform a chewing task whilst having a functional MRI may reveal different impacts of tooth loss to these regions.

Despite the findings of the current study, there may be alternative explanations for the observed association between tooth loss and regional GMV change. Firstly, periodontitis is one of the main causes of tooth loss in older adults [45]. Therefore, tooth loss may be regarded as a crude marker of periodontitis experience. There is strong evidence that periodontitis represents a source of chronic low-grade inflammation, which contributes to the cumulative systemic inflammatory burden [46,47]. Persistent inflammation in the systemic immune system can impose detrimental effects on the central nervous system [48], including GMV change [49]. Periodontitis has also recently been associated with higher levels of tau protein [50], and plasma levels of amyloid beta $(A\beta)^{1-42}$ and $A\beta^{1-40}$ [51], which may reinforce an inflammatory hypothesis. Secondly, periodontitis and by extension tooth loss has also been associated with a number of other inflammatory based systemic diseases including diabetes [52], coronary heart disease [53], and hypertension [54]. These three conditions have previously been associated with GMV change [55–57], and may therefore represent an indirect pathway between periodontitis / tooth loss and GMV change. In the current study, we attempted to control for this by adjusting for these conditions in our multi-variable analysis. However, it is acknowledged there may be risk of residual confounding or the influence of undiagnosed co-morbidities which may affect the observed observation. Thirdly, tooth loss may be associated with an impaired chewing ability, potentially affecting food choices and leading to a poorer nutritional status [58]. Diet and diet quality have been shown to have an effect on brain GMV [59,60]. However, severe masticatory impairment causing a shift in food selection is generally only observed when few teeth or no teeth remain and subjects fail to adapt to dentures [61]. In the current study, all participants in the edentulous group wore complete dentures which limits the ability to draw conclusion regarding severe masticatory impairment. Furthermore, a recent review concluded that evidence relating to the effect of tooth loss on diet and nutrition is weak, with inconsistent results among the few studies identified [62]. Fourthly, the underlying

assumption of the hypothesis investigated was loss of natural teeth negatively impacts somatosensory feedback associated with mastication. Yet some studies have shown that masticatory function is not always dependent on the number of teeth [63]. Moreover, the prosthetic replacement of lost teeth may also have an influence in the plasticity of such somatosensory feedback mechanisms [18]. It has been shown that the treatment of total tooth loss (edentulism) with complete dentures increases the occlusal contact area and increases occlusal force. This situation leads to an increase in brain functional activity measured with electroencephalography [64].

Strengths of the study include the relatively large sample size (n=380) which ranks comparatively as one of the largest human studies investigating tooth loss and regional GMV change [24,25,33]. The exposure variable, tooth loss, was comprehensively assessed by a detailed full-mouth dental examination by a trained and calibrated dentist. The outcome variable, regional GMV, was assessed using Freesurfer utilities which is a well-established technique for automatically performing neuroanatomical labelling and has previously been shown to be valid and highly accurate with a mean distance error of <1 mm [31]. A further strength relates to the design of the TILDA study with its main aim to investigate factors associated with population ageing. We were therefore able to make use of a wide range of relevant data on potential confounding factors. In our statical models we were able to control for a large range of variables (including age, sex, education, head size, BMI, exercise, smoking, alcohol, co-morbidities, SES, marital status, and depression) suggesting that these factors did not account for the observed findings.

Limitations with this study include firstly, that the study is a cross-sectional study and as such, it is not possible to determine whether tooth loss causally contributed to regional GMV decrease or was a consequence of it. Although associations were observed after adjusting for a range of potential confounders, the cross-sectional design precludes assessment of any temporal relationships between tooth loss and GMV change. To investigate temporality and direction of an association, the observations in this study would need to be confirmed with prospective studies. Secondly, there is selection bias based in the recruitment strategy of participants into the study. Although the TILDA study used a nationally representative sampling strategy, the health assessments including the oral health assessments and MRI sub-study, required participants to attend dedicated research centres in Dublin. Participants who were not mobile or well enough would not likely have attended the in-person health assessments or MRI sub-study. Subjects included in the current study were less likely to be smokers, had a higher educational achievement, and had a higher SES background than those in the general cohort of the study (Supplementary Information, Table S1). A further form of selection bias relates to the inclusion criteria used for entry into the study. Individuals were not eligible if they reported a doctor's diagnosis of dementia or were not able to consent because of severe cognitive impairment. However, by excluding these participants, where GMV change associated with cognitive decline may have been more apparent, the strength of an association between tooth loss and GMV change may have potentially been weakened. Finally, in common with all observational studies, the possibility of residual confounding such as aging or the failure to account for other relevant confounders may have had some influence on the reported association between tooth loss and GMV change.

5. Conclusion

In conclusion, tooth loss was associated with reduced regional GMV in a group of 380 community-dwelling older adults from Ireland. Regions that consistently associated with tooth loss included the paracentral lobule and the cuneus cortex. This relationship was independent of known confounders and as such could reflect the possibility that tooth loss may be a risk factor for reduced GMV. Alternatively, there may be shared biological pathways leading to both tooth loss and reduced GMV. Further, longitudinal type studies should be aimed at specifically investigating potential causality and the mechanistic process linking tooth loss and GMV change. Additionally, randomised controlled trails are required to investigate whether treatment of the causes of tooth loss (eg. periodontitis), or treatment of the consequences of tooth loss (eg. prosthodontic rehabilitation) might have a beneficial impact on GMV change.

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CRediT authorship contribution statement

Lewis Winning: Conceptualization, Formal analysis, Methodology, Writing – original draft. **Céline De Looze:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Silvin P. Knight:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Daniel Carey:** Methodology, Writing – review & editing. **James F. Meaney:** Funding acquisition, Methodology, Writing – review & editing. **Rose Anne Kenny:** Conceptualization, Funding acquisition, Writing – review & editing. **Brian O'Connell:** Conceptualization, Funding acquisition, Writing – review & editing.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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