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ORIGINAL RESEARCH

Incidental findings on cerebral MRI in twins: the Older Australian Twins Study

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Abstract Incidental findings on structural cerebral magnetic resonance imaging (MRI) are common in healthy subjects, and the prevalence increases with age. There is a paucity of data regarding incidental cerebral findings in twins. We examined brain MRI data acquired from community-dwelling older twins to determine the prevalence and concordance of incidental cerebral findings, as well as the associated clinical implications. Participants (n = 400) were drawn from the Older Australian Twins Study. T1-weighted and T2-weighted fluid-attenuated inversion recovery (FLAIR) cerebral MRI scans were systematically reviewed by a trained, blinded clinician. Incidental findings were recorded according to pre-determined categories, and the diagnosis confirmed by an experienced neuroradiologist. Periventricular and deep white matter hyperintensities (WMH) were scored visually. WMH heritability was calculated for those with the twin pair included in the study (n = 320 individuals; monozygotic (MZ) = 92 twin pairs, dizygotic (DZ) = 68 twin pairs). Excluding infarcts and WMH, a total of 47 (11.75%) incidental abnormalities were detected. The most common findings were hyperostosis frontalis interna (8 participants; 2%), meningiomas, (6 participants; 1.5%), and intracranial lipomas (5 participants; 1.25%). Only 3% of participants were referred for follow-up. Four twin pairs, all monozygotic, had lesions concordant with their twin. Periventricular WMH was moderately heritable (0.61, CI 0.43–0.75, p = 7.21E-08) and deep WMH highly heritable (0.80, CI 0.66–0.88, p = 1.76E-13). As in the general population, incidental findings on cerebral MRI in older twins are common, although concordance rates are low. Such findings can alter the clinical outcome of participants, and should be anticipated by researchers when designing trials involving cerebral imaging.

Keywords Incidental findings · Cerebral magnetic resonance imaging · Older twins

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Introduction

Structural magnetic resonance imaging (MRI), widely used in research studies of community based cohorts, can reveal incidental findings in asymptomatic individuals. Previous studies have demonstrated that incidental brain findings are commonly detected in healthy pediatric (Gur et al. 2013), general adult (Håberg et al. 2016; Vernooij et al. 2007) and older community-dwelling subjects (Sandeman et al. 2013; Al-Holou et al. 2011). In an international systematic review of 19,559 adults who underwent a brain MRI for occupational, clinical or commercial screening, the crude prevalence of incidental findings was 2.7% (Morris

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et al. 2009). The prevalence of neoplastic incidental brain findings, including meningiomas (Vernooij et al. 2007), infarcts and white matter hyperintensities (Morris et al. 2009), have been shown to significantly increase with age.

When examining the prevalence of incidental findings on brain MRI specifically in older adults, there is significant variability in the current literature. The PROOF study (Boutet et al. 2017) found 77.9% of their 503 participants (over 70 years of age) had an incidental finding, the majority of which were cysts (45.9%) and ear, nose and throat (ENT) anomalies (24.8%). Another cohort study (n = 700) found that the prevalence of incidental findings in adults over 65 years was closer to 30% (Sandeman et al. 2013); 61% of these were stroke-related, and a further 34% were attributed to ENT abnormalities. Conversely, the PATH Through Life study (Kumar et al. 2008) detected abnormalities in 4.8% subjects aged 60–64 years old, although this excluded stroke-related and ENT anomalies. Such discrepancies may therefore in part be explained by differences in the categories of incidental findings reported and age range of participants. It has also been demonstrated that the prevalence of incidental findings on MRI increases with magnetic field strength (Morris et al. 2009).

Such findings are potentially distressing to the individual, and can be difficult to manage in a research setting. Whilst population-based MRI studies provide an invaluable opportunity to determine the prevalence of radiological abnormalities, they also highlight the need to consider the associated clinical and ethical issues. Although the detection of incidental findings in healthy subjects recruited to research is common, those with clinical consequences are generally reported to comprise 2–15% of those findings, but are rarely urgent (Yue et al. 1997; Bos et al. 2016; Boutet et al. 2017; Håberg et al. 2016). Nevertheless, for a small proportion of individuals, the findings warrant further evaluation and intervention. Therefore, investigators must anticipate and have clear guidelines on how to approach these findings, in order to prevent unnecessary anxiety to the individual, and costs to the health system (Illes et al. 2008).

The twin pair method is a classic design to investigate the relative influence of environmental and genetic factors on a phenotype. Our group has previously reported on the heritability for a number of structural brain measures, including global and lobar cortical volumes (Batouli et al. 2014), cortical and subcortical grey-matter volumes (Wen et al. 2016), and white matter hyperintensity volumes (Sachdev et al. 2016) in a cohort of older Australian twins. Twin studies have also estimated the heritability of other structural measures such as brain surface area and cortical thickness (Jansen et al. 2015). To date, there has been no investigation into the prevalence and concordance of incidental cerebral findings in twins, despite being a commonly targeted cohort for research. We examined brain MRI data acquired from community-dwelling older twins to determine the prevalence and concordance of incidental cerebral findings in this specific cohort, as well as the medical implications of these findings.

Materials and methods

Participants

Participants were drawn from the Older Australian Twins Study (OATS), the methodology of which has been previously described in detail (Sachdev et al. 2009). The OATS is a longitudinal, population-based study of twins registered with the Australian Twin Registry (www.twins.org.au) aged 65 years or older, who were invited by mail to participate followed by a telephone screening. Subjects were excluded if they had a diagnosed malignancy or other life-threatening medical illness, acute psychotic illness, or an intellectual disability. Subjects underwent comprehensive clinical assessment. Those who consented and had no contraindications (such as an implantable device, magnetic foreign body or cardiac pacemaker) were invited to undergo a brain MRI scan. Participants received a comprehensive assessment (as outlined below) at baseline and every two years; for the purpose of this particular study, only participants with cerebral imaging completed at baseline (wave 1) were included. Participants provided written informed consent.

Clinical data

Participants were interviewed by trained research assistants for baseline demographic and clinical information, including a history of physician-diagnosed vascular risk factors such as hypercholesterolemia, diabetes and hypertension (mean systolic BP ≥ 160 mmHg or mean diastolic BP ≥ 95 mmHg). Obesity was measured using the body mass index (BMI). History of previous myocardial infarct, stroke and atrial fibrillation diagnosed by a physician were also recorded, as well as previous diagnoses of malignancy, cerebral infection, migraine, epilepsy, and severe head injury (that is, head injury with a loss of consciousness).

Cerebral MRI acquisition and preparation for visual examination

MRI data were obtained from three centers for 400 of the total 623 wave 1 participants. In Melbourne, a 1.5 T Siemens Magnetom Avanto scanner (N = 148) was used. In Brisbane, a 1.5 T Siemens Sonata (N = 102) (Siemens Medical Solutions, Malvern, PA, USA) of similar manufacturer specifications was used. In Sydney, a Phillips 1.5 T Gyroscan scanner (Philips Medical Systems, Best, The Netherlands) was initially used (N = 116) and was later replaced by a Philips 3 T Achieva Quasar Dual scanner (N = 34). Acquisition protocols were matched across the centers (Sachdev et al. 2009). Twins were always scanned in the same scanner, either on the same day or within a few weeks of one another.

Both 3D T1-weighted scans and T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence scans were used for visual examination. The following protocol was used for T1-weighted MRI scans on the 1.5 T scanners in all three centers: in-plane resolution 1 × 1 mm with slice thickness of 1.5 mm, contiguous slices, TR/TE/TI = 1530/3.24/780 ms, and flip angle = 8. FLAIR scans were acquired axially with the same acquisition parameters on the 1.5 T scanners in all three centers, i.e. TR/TE/TI = 10,000/120/2800 ms, with slice thickness 3.5 mm and in-plane resolution 0.898 × 0.898 mm2. On the 3 T scanner in Sydney, we had spatial resolution of 1 × 1 × 1 mm3, TR/TE = 6.39/2.9 ms for T1-weighted scans, and TR/TE/TI = 10,000/110/2800 ms, with slice thickness 3.5 mm and in-plane resolution 0.898 × 0.898 mm2 for FLAIR scans. We co-registered T1-weighted and FLAIR images of the same participant in order to view them simultaneously using Statistical Parametric Mapping, 8th version (SPM8) (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK, 2009).

All scans were systematically reviewed for incidental findings by a Neuropsychiatry Fellow (RK) with 5 years of experience in reading brain MRIs, who had also had additional neuroradiology training exposure. The T1-weighted and FLAIR images for each participant were viewed simultaneously and systematically, using the MRIcron for Windows (Rorden 2015) software. RK was blinded to all participants' demographic and clinical information, as well as twin status during the reviews. Periventricular and deep white matter hyperintensities (PWMH and DWMH) were scored using a well-validated and widely used visual rating, the Fazekas scale (Fazekas et al. 1987), from 0 (absent) to 3 (severe). PWMH and DWMH were also binarized into absent (Fazekas score of 0) or present (Fazekas score of 1–3).

A senior neuropsychiatrist (AM), with more than 10 years' experience in reviewing brain MRIs, reviewed 50 scans independently to check reliability. Both ambiguous and definite lesions were then reviewed by a neuroradiologist (LD) who was also blinded to the participant history and clinical information. Inter-rater reliability was moderate according to Cohen's kappa (κ) for both PWMH (Cohen's $\kappa = 0.687$, $p < 0.01$) and DWMH (Cohen's $\kappa = 0.673$, $p < 0.01$) Fazekas scores. Inter-rater reliability for other incidental findings was unable to be calculated due low numbers for each variable. Abnormal incidental findings were subsequently cross-checked against study files. GPs and subjects were contacted if follow-up was required.

Statistical analysis

Any structural findings were categorized into pre-specified pathological territories: cortical infarcts, lacunar infarcts, neoplasms (benign, malignant or metastatic), cysts, vascular abnormalities, bony abnormalities, developmental anomalies or "other" if unable to be categorically determined. ENT-related incidental findings were not included in this study. The Fazekas PWMH and DWMH ratings were analyzed separately. T-tests were used to test the equality of means between the two zygosity groups for continuous measurements, and chi-squared tests for categorical measures. The *p*-values were obtained by 10,000 permutations. Frequency analyses were conducted to assess the rates of incidental findings on all participants with a baseline MRI ($n = 400$). All the analyses were completed using R 3.2.2 for Windows (R Core Team 2015) software.

Structural equation modeling (SEM) was used to estimate the heritability of the PWMH and DWMH in all twin pairs without missing data ($n = 320$). In the SEM, the variance of the phenotype is decomposed into additive genetic (A), shared environmental (C) and unique environmental (E) components. The heritability is estimated as the ratio of additive genetic variance to the total variance. To test the model parsimony, the likelihoods of the models containing the variance components A and E (AE), C and E (CE), and E were compared with the likelihood of the full ACE model. The WMH were analyzed in two different ways: Binarized WMH (0 if absent and 1 if present) and multiple category (Fazekas score of 0–3). Heritability estimates for binary and Fazekas scores were obtained using the liability threshold models (Rijsdijk and Sham 2002). The heritability analyses adjusted for the covariates age, sex and scanners were performed using the SEMs for twin data as implemented in the R package OpenMx version 2.0 (Neale et al. 2016). Because the rates of other incidental findings within each category were low, we were unable to calculate the heritability in a statistically meaningful way.

Results

Sample characteristics

Table 1 compares the clinical characteristics of all monozygotic (MZ; $n = 221$ individuals; mean age 70.39 ± 5.23 years; 138 (62.44%) females) and dizygotic (DZ; $n = 179$ individuals; mean age 70.31 ± 4.87 years; 122 (68.16%) females) twins who obtained an MRI. There were no statistically significant differences in mean age, sex, years of education or any of the clinical parameters between the MZ and DZ groups (Table 1). Of the 400 participants, 320 had their co-twin included in the study: 92 MZ twin pairs (mean age 70.28 ± 5.13 years; 59 MZ female pairs) and 68 DZ twin pairs (mean age 69.98 ± 4.62 years; 35 DZ female, 8 DZ male, 25 DZ opposite sex pairs).

Rates and concordance of incidental abnormalities on brain MRI in twins

Table 2 compares the rates of incidental abnormalities found in all MZ and DZ twins who obtained a brain MRI (combined

Table 1 Sample characteristics (n = 400)

	MZ (n = 221) n (%)	DZ (n = 179) n (%)	p-value
Sex (females)	138 (62.44)	122 (68.16)	0.09
Mean age in years (SD)	70.39 (5.23)	70.31 (4.87)	0.87
Years education (SD)	11.33 (3.43)	11.39 (3.43)	0.87
Mean BMI	26.47 (4.62)	26.48 (3.98)	0.99
History of			
Stroke	10 (4.55)	7 (3.93)	0.57
Myocardial infarct	16 (7.27)	7 (3.93)	0.14
Atrial fibrillation	13 (6.1)	5 (2.90)	0.09
Hypertension	117 (53.42)	94 (53.11)	0.92
High cholesterol	118 (54.38)	92 (51.68)	0.54
Type 2 diabetes	25 (11.36)	17 (9.55)	0.52
Migraine	44 (20.09)	36 (20.22)	0.90
Cancer*	26 (11.87)	18 (10.06)	0.52
Brain infection	7 (3.18)	4 (2.26)	0.55
Epilepsy	3 (1.36)	3 (1.68)	0.98
Severe head injury	26 (12.38)	23 (13.07)	0.76

For categorical measures, n (%) are presented. *denotes cancer of any kind, excluding skin cancer. *MZ*, monozygotic; *DZ*, dizygotic; *SD*, standard deviation; *BMI*, Body Mass Index

total of n = 400). Excluding infarcts and WMHs, a total of 47 (11.75%) incidental abnormalities were detected. Hyperostosis frontalis interna was the most common finding (eight participants; 2%), followed by meningiomas, (six participants; 1.5%), and then intracranial lipomas (five participants; 1.25%). Because rates of incidental findings within each category were low, we were unable to analyze differences in MZ and DZ in a statistically meaningful way, although the results are summarized in Table 2.

Of the 320 participants with their twin pair included in the study, 36 individuals (MZ = 22, DZ = 14) had incidental findings. As in the total sample, hyperostosis frontalis interna (MZ = 5, DZ = 3) was the most common incidental finding in the paired sample, followed by lipoma (MZ = 3, DZ = 1), cavum septi pellucidi (MZ = 2, DZ = 1), and meningioma (MZ = 0, DZ = 3). Of the 36 with incidental findings, only eight individuals (that is, four twin pairs, all MZ) had the lesion concordant in their co-twin: one pair with hyperostosis frontalis interna, one pair with corpus callosum dysgenesis, one pair with cavum septi pellucidi, and one pair with empty sella.

Incidental findings referred for follow-up

Twelve (3%) of the participants were referred for clinical follow-up. Two with normal pressure hydrocephalus (NPH)-like lesions were referred for neurosurgical review, of which one required treatment with a ventriculoperitoneal shunt. The two participants with malignant tumors and one with an aneurysm were also referred for urgent neurosurgical assessment. A participant with a subependymoma was referred and eventually underwent neurosurgical excision. Four participants with a meningioma and two with a cavernous hemangioma were also referred for further evaluation.

Rates and concordance of cerebrovascular pathology on MRI scans in twins

Of the whole sample, 22 participants (5.50%) had one or more lacunes, and 11 participants (2.75%) had cortical infarcts (Table 3). There were no statistically significant differences in these rates between MZ and DZ twins.

Evidence of periventricular WMH was apparent in 255 of the 400 participants (63.75%), of which 165 (41.25%) were mild, 60 (15%) were moderate, and 30 (7.5%) were severe, according to the Fazekas visual rating. 287 of the 400 participants (71.75%) had evidence of deep WMH, of which 215 (53.75%) were mild, 60 (15%) were moderate and 12 (3%) were severe. There were no statistically significant differences in rates of either periventricular or deep WMH between MZ and DZ twins (Table 3).

Of the 320 with a paired twin brain MRI included in the study, 19 individuals had lacunes (MZ = 13, DZ = 6) and six (MZ = 3, DZ = 3) had cortical infarcts. Of these vascular lesions, only four individuals (that is, two twin pairs, both MZ) had a lacunar infarct concordant in the twin pair.

Heritability of periventricular and deep WMH

A full ACE model was initially fitted with age, sex and scanners as covariates for the 320 participants with their paired

Table 2 Rates of incidental abnormalities on cerebral MRI in twins (n = 400)

Radiological diagnosis	Total (n = 400) n (%)	MZ (n = 221) n (%)	DZ (n = 179) n (%)
Primary tumor, benign			
Intracranial lipoma	5 (1.25)	3 (1.36)	2 (1.12)
Meningioma	6 (1.50)	2 (0.90)	4 (2.23)
Subependymoma	1 (0.25)	0 (0.00)	1 (0.56)
Primary tumor, malignant			
Glioma	1 (0.25)	1 (0.45)	0 (0.00)
Cystic neoplasm, undifferentiated	1 (0.25)	1 (0.45)	0 (0.00)
Cysts			
Arachnoid	3 (0.75)	3 (1.36)	0 (0.00)
Hippocampal	1 (0.25)	1 (0.45)	0 (0.00)
Vascular (excluding infarcts)			
Aneurysm	1 (0.25)	1 (0.45)	0 (0.00)
Cavernous hemangioma	2 (0.50)	1 (0.45)	1 (0.56)
Other developmental anomalies			
Corpus callosum dysgenesis	3 (0.75)	2 (0.90)	1 (0.56)
Cavum septum pellucidum	4 (1.00)	2 (0.90)	2 (1.12)
Empty sella	2 (0.50)	2 (0.90)	0 (0.00)
Bony lesions			
Hyperostosis frontalis interna	8 (2.00)	5 (2.26)	3 (1.68)
Acromegaly	2 (0.50)	1 (0.45)	1 (0.56)
Ventricular lesions			
NPH-like lesion	2 (0.50)	2 (0.90)	0 (0.00)
Xanthogranuloma	1 (0.25)	0 (0.00)	1 (0.56)
Other			
Ossified falx	2 (0.50)	1 (0.45)	1 (0.56)
Non-specific gliosis	1 (0.25)	1 (0.45)	0 (0.00)
Basal ganglia calcification	1 (0.25)	0 (0.00)	1 (0.56)
TOTAL	47 (11.75%)	29 (13.12%)	18 (10.06%)

NPH, normal pressure hydrocephalus

Table 3 Cerebrovascular pathology on MRI scans in twins (n = 400)

	Total (n = 400) n (%)	MZ (n = 221) n (%)	DZ (n = 179) n (%)	p-value
Infarcts				
Cortical	11 (2.75)	5 (2.26)	6 (3.35)	0.36
Lacunar	22 (5.50)	14 (6.33)	8 (4.47)	0.38
Fazekas[a] periventricular WMH rating				
0	145 (36.25)	83 (37.56)	62 (34.64)	0.68
1	165 (41.25)	93 (42.08)	72 (40.22)	
2	60 (15.00)	31 (14.03)	29 (16.20)	
3	30 (7.50)	14 (6.33)	16 (8.94)	
Fazekas deep WMH rating				
0	113 (28.25)	66 (29.86)	47 (26.26)	0.38
1	215 (53.75)	120 (54.30)	95 (53.07)	
2	60 (15.00)	31 (14.03)	29 (16.20)	
3	12 (3.00)	4 (1.81)	8 (4.47)	

For categorical measures, n (%) are presented. *MZ*, monozygotic; *DZ*, dizygotic; *WMH*, white matter hyperintensities

[a] Fazekas et al. 1987

Table 4 Heritability of periventricular and deep white matter hyperintensities (n = 320)

Trait	A (CI)	E (CI)	p-value AE	p-value CE	p-value E	p-value AE h^2
FazPWM	0.61 (0.43, 0.75)	0.39 (0.25, 0.57)	0.592291	0.11057	4.36E-07	7.21E-08
FazDWM	0.80 (0.66, 0.88)	0.20 (0.12, 0.34)	1	0.000107	1.66E-12	1.76E-13
BiFazPVWM	0.70 (0.45, 0.86)	0.30 (0.14, 0.55)	0.619418	0.222388	6.48E-06	1.16E-06
BiFazDWM	0.91 (0.77, 0.98)	0.09 (0.02, 0.23)	0.970791	0.004498	2.64E-11	2.96E-12

FazPVWM, Fazekas periventricular white matter hyperintensity rating; *FazDWM*, Fazekas deep white matter hyperintensity rating; *BiFaz*, binarized version of the Fazekas rating (0 if absent, 1 if present); *CI*, confidence interval

"A" refers to heritability, the variance explained by the additive genetic component. "E" refers to the variability attributed to the unique environment. Under the AE model this is also equivalent to intra-class correlation among the MZ pairs and half of this component is the intra-class correlation among the DZ pairs. The last 4 columns are the p-values for comparison of the AE (p-value AE), CE (p-value CE), E (p-value E) with full ACE model. Comparison of AE with E (p-value AE h^2) is also the p-value for heritability value under the AE model

twin brain MRI included in the study. Age was found to be the only significant covariate, and Table 4 shows the heritability estimates. Periventricular WMH was moderately heritable (0.61, CI 0.43–0.75, p = 7.21E-08) and deep WMH highly heritable (0.80, CI 0.66–0.88, p = 1.76E-13). Heritability increased under a binary model (i.e. absent or present): 0.70 (CI 0.45–0.86, p = 1.16E-06) for periventricular WMH and 0.91 (CI 0.77–0.98, p = 2.96E-12) for deep WMH.

Discussion

Asymptomatic, incidental findings on cerebral MRI scans have been widely reported in population-based studies (Morris et al. 2009; Håberg et al. 2016; Vernooij et al. 2007). This study is the first to investigate the prevalence and concordance of incidental findings on cerebral MRI scans of elderly twins. Overall, 11.75% of participants had an incidental finding, excluding cerebrovascular pathology (that is, lacunes, cortical infarcts and WMH). Although no study is strictly comparable owing to differences in sample acquisition and age range, this rate is much higher than the large meta-analysis of all neuroimaging studies (3%), although the mean age of this meta-analysis population was significantly younger (Morris et al. 2009). Our results demonstrated a similar rate of incidental findings to the large, Rotterdam population-based study of older subjects (9.5% of 5800 participants, mean age 64.9 years (Bos et al. 2016)). Our prevalence rates are lower than the Lothian birth cohort of a similar mean age (72.5 years) which identified 32% of their 700 participants had an incidental finding (Sandeman et al. 2013). This discrepancy can be explained by differences in classification; we have separated vascular pathology (whereas infarcts (including lacunes) and microhemorrhages account for 12% and 6% of their participants, respectively), as well as excluded ENT problems (10.9% of their participants).

Hyperostosis frontalis was the most common finding in our sample (2%), which is significantly lower than the 5–12% rate reported in the general population (She and Szakacs 2004). Meningiomas were the second most frequently found incidental lesion (1.5%), the prevalence of which could be expected between those found in a younger population (0.29% prevalence in the systematic review (Morris et al. 2009) and nonagenarians (3.95%) (Al-Holou et al. 2011). Aneurysms (0.25%), however, were less common than reported in the Rotterdam population based study (2.3%) (Bos et al. 2016). Differences may be a consequence of our sample composition and smaller size, the imaging sequences examined, and differences in the methods used by and experience of reviewers.

Only eight individuals (that is, four twin pairs, all MZ) had the lesion concordant in their twin: one pair with hyperostosis frontalis interna, one pair with corpus callosum dysgenesis, one pair with cavum septi pellucidi (Fig. 1) and one pair with empty sella. The literature suggests that empty sella syndrome (ESS) is not typically heritable; there is one case report describing its occurrence in a father and two children (Colliot et al. 1990), and we are uncertain if in our study this twin pair represents a case of primary or secondary ESS. Cavum septi pellucidi (CSP) is present at birth as a feature of normal development, but has an estimated prevalence of 12–20% in adults (Sarwar 1989). There is little in the literature regarding the heritability of persisting CSP, although one study of 48 male monozygotic twins discordant for combat exposure has estimated the heritability of CSP to be 12% (May et al. 2004). Dysgenesis of the corpus callosum may occur in isolation or more commonly as part of a neurodevelopmental disorder, particularly chromosomal (autosomal and X-linked) syndromes (Bedeschi et al. 2006). A large population-based study identified a prevalence rate of corpus callosal dysgenesis at 1.8 per 10,000 live births, of which 17.3% were associated with an identifiable chromosomal abnormality, particularly aneuploidy (Glass et al. 2008). In keeping with the previous literature, there have been a small number of case reports of dysgenesis of the corpus callosum in MZ twins, and the concordance is estimated to be less than 50% (Chitrit et al. 2009).

Lacunes were found in 5.5% of participants, and cortical infarcts found in 2.75% of participants. This is comparable with other community based studies: in the larger PROOF study, lacunes were found in 5.4% or participants, and cortical

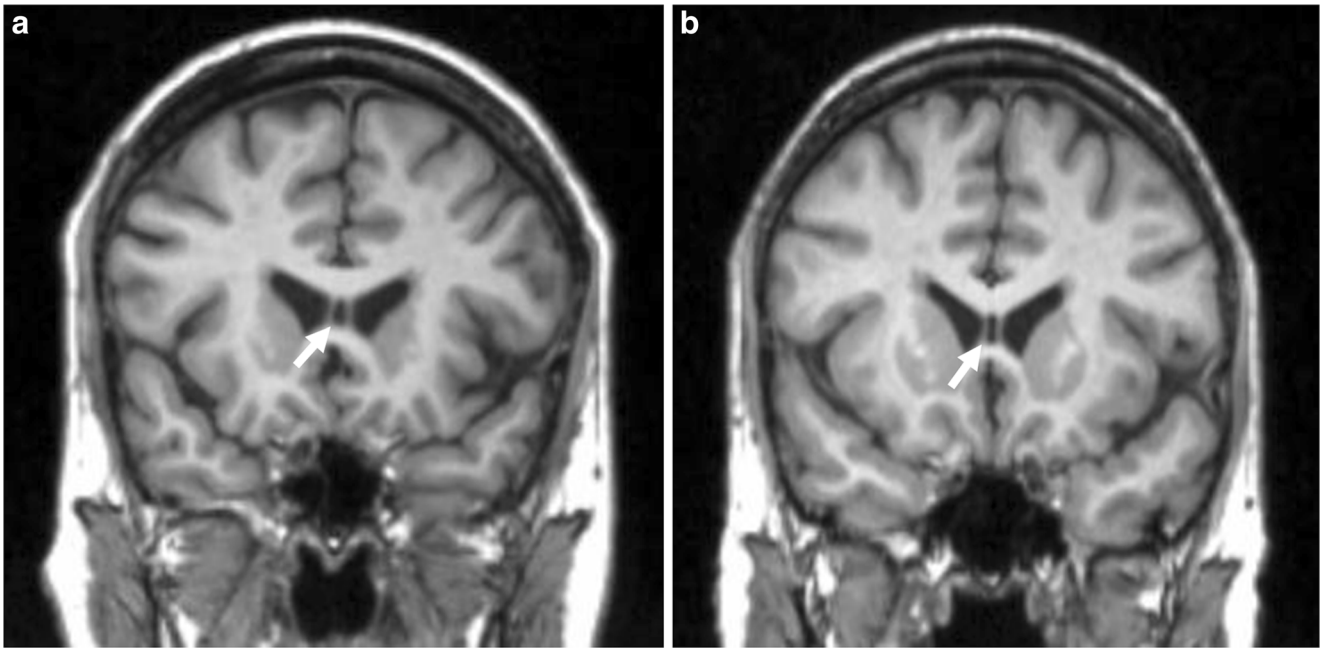

Fig. 1 Monozygotic twin pair concordant for cavum septi pellucidi (*white arrows*)

infarcts found in 1.2% (Boutet et al. 2017). The PATH Through Life Study suggested the prevalence of lacunes in an elderly community sample (60–64 years of age) was 7.8% (Chen et al. 2009). Of the vascular lesions, only four individuals (that is, two twin pairs, both MZ) had a lacunar infarct concordant in the twin pair. Their concordance specifically in MZ twins is supported by previous findings that lacunes are highly heritable (Traylor et al. 2015).

Whilst incidental findings were common in this sample, only 12 of these lesions were referred for follow-up of potential clinical significance. This is consistent with previous findings that have demonstrated that whilst incidental findings on cerebral MRI are common, clinically serious abnormalities are rare (Sandeman et al. 2013; Bos et al. 2016; Yue et al. 1997). Nevertheless, MRI findings may influence treatment decisions, and may be a source of anxiety and burden of further medical follow-up. It may be assumed that such findings will be disclosed to subjects, but there is significant variability in the procedures for management across research centers, including the communication of findings, training and specialist neuroradiologist involvement (Illes et al. 2004). There are ethical implications under the principles of *primum non nocere* (first, do no harm) and duty of care, as well as a legal liability, which varies considerably internationally (Leung 2013). This study highlights the importance for both clinicians and researchers of having a standardized set of guidelines for managing incidental findings to minimize the risk of jeopardizing subject welfare, in keeping with previous recommendations in the literature (Illes et al. 2008). Additionally, by demonstrating a higher concordance of some findings in MZ twins, it suggests implications for the co-twin in which one twin is imaged in a research or clinical setting. We recommend that if the imaged twin agrees, the co-twin should be offered an opportunity to discuss the findings and their potential implications.

White matter hyperintensities (WMH) were extremely common in this study population. Periventricular WMH (PWMH) were found in 63.75% of the total sample, and deep WMH (DWMH) were found in 71.75% (Fig. 2). WMH are a common finding with increasing age and have previously been well-described in the literature (Longstreth et al. 1996; Boutet et al. 2017; Wen and Sachdev 2004). A relative strength of this particular study was in examining the heritability of both periventricular and deep WMH. The heritability of both PWMH (0.61) and DWMH (0.80) was high, and extremely high when examined under a binarized model (PWMH 0.70 and DWMH 0.91). This is consistent with previous volumetric studies in male twins with a mean age of 72 years (heritability estimate of 0.71) (Carmelli et al. 1998), as well as a volumetric MRI study of the same sample completed by our own group (total WMH volume heritability estimate of 0.76) (Sachdev et al. 2016). Our visual ratings therefore provide evidence from an alternative perspective that WMH are indeed under strong genetic influence.

Limitations

The current study has several limitations. The sample size is small, and may be inadequately powered to detect the broader scope of possible incidental findings. Rates within each category are low, which limits our capacity to report meaningfully

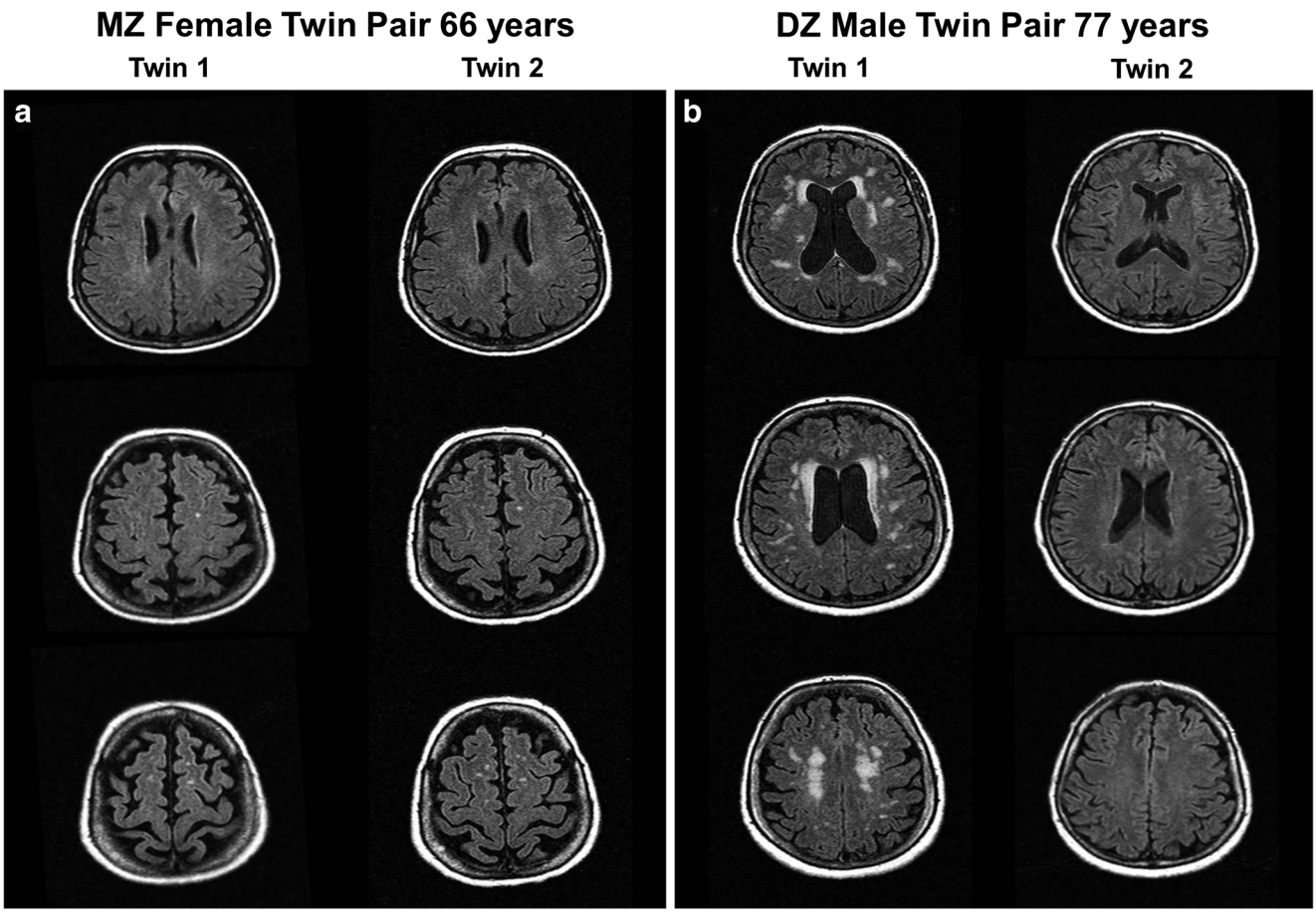

Fig. 2 Example of white matter hyperintensities (WMH) in (**a**) a monozygotic (MZ) twin pair concordant for periventricular and deep WMH, and (**b**) a dizygotic (DZ) twin pair discordant for WMH, with the twin on the left diagnosed with hypertension and hypercholesterolemia. [Each vertical panel contains images from one cerebral T2-FLAIR MRI scan]

on concordance of incidental findings in the twin population. Moreover, the sample was made up of volunteers from the Australian Twin Registry and perhaps only more motivated individuals are likely to volunteer, thereby introducing selection bias; therefore, we cannot be certain of how representative these results are of the elderly twin population. The current study is also limited to a cross-sectional snapshot; future work may take advantage of the longitudinal study design of the OATS to more closely examine the development of incidental findings in twin pairs over time.

The imaging was limited to T1- and T2-FLAIR sequences only, which would restrict the type of lesion that could be visualized and potentially lead to an underestimate of incidental findings, and may explain differences in rates of incidental findings compared to other studies. Susceptibility-weighted imaging, for example, would have increased the sensitivity to detect microhemorrhages and calcifications (Liu et al. 2016). Moreover, there is arguably more room for error in the visual rating of WMH compared to volumetric studies, although the consistency with volumetric studies completed with our group (Sachdev et al. 2016) is reassuring.

Conclusions

Incidental findings on cerebral MRI in older twins are common, although no more so than in the general population. Such findings can alter the clinical outcome of participants, and should be anticipated by researchers when designing trials involving cerebral imaging. Practical and ethical consideration should be given to the management of such findings, particularly given the advances in magnetic resonance imaging technology in the context of our aging population.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval The Older Australian Twins Study obtained approval from the ethics committees of the Australian Twin Registry, University of New South Wales, University of Melbourne, Queensland Institute of Medical Research, University of Queensland, and the South Eastern Sydney & Illawarra Area Health Service.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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