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Mixed handedness is associated with greater age-related decline in volumes of the hippocampus and amygdala: the PATH through life study

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Abstract

Handedness has been found to be associated with structural and functional cerebral differences. Left handedness and mixed handedness also appear to be associated with an elevated risk of some developmental and immunological disorders that may contribute to pathological processes developing in ageing. Inconsistent reports show that left handedness may be more prevalent in early-onset as well as late-onset Alzheimer's disease, but might also be associated with slower decline. Such inconsistencies may be due to handedness being usually modeled as a binary construct while substantial evidence suggests it to be a continuous trait. The aim of this study was to investigate the relationship between brain structures known to be implicated in pathological ageing and strength and direction of handedness. The association between handedness and hippocampal and amygdalar atrophy was investigated in 327 cognitively healthy older individuals. Handedness was measured with the Edinburgh Inventory. Two measures were computed from this index, one reflecting the direction (left = 0/right = 1) and the other the degree of handedness (ranging from 0 to 1). Hippocampal and amygdalar volumes were manually traced on scans acquired 4 years apart. Regression analyses were used to assess the relationship between strength and direction of handedness and incident hippocampal and amygdalar atrophy. Analyses showed that strength but not direction of handedness was a significant predictor of hippocampal (Left: beta = 0.118, $P = 0.013$; Right: beta = 0.116, $P = 0.010$) and amygdalar (Right: beta = 0.105, $P = 0.040$) atrophy. The present findings suggest that mixed but not left handedness is associated with greater hippocampal and amygdalar atrophy. This effect may be due to genetic, environmental, or behavioural differences that will need further investigation in future studies.

Introduction

Handedness is an important aspect of human psychology, however, its origins, neurobiological substrates, and function are not well understood. Apart from obvious functional differences, subtle cognitive and behavioral differences have been demonstrated in relation to various handedness measures (Cherbuin and Brinkman 2006; Leask and Crow 2006; Siengthai et al. 2008) but their ecological significance is uncertain. In this paper, we will review the available evidence investigating a link between handedness and short- and long-term biological and cognitive vulnerabilities, and we will test such an association in a large sample using a longitudinal design less open to bias than cross-sectional investigations.

A number of competing theories have been developed to account for handedness differences in humans. A main genetic origin of handedness is widely accepted and Annett's and McManus' theories of a single gene, two-allele determinant of handedness have accumulated substantial supporting evidence. Annett (1998) proposed that a gene responsible for handedness phenotype could present either with a dominant allele for handedness direction (RS+), which shifts handedness to the right or a neutral allele (RS−), which leaves direction of handedness to chance. Thus, according to

Annett, carrying two RS+ alleles would be associated with a shift of approximately two standard deviations to the right while one allele would be associated with a one standard deviation shift. The McManus' (1985, 2002) theory is very similar to Annett's but diverges in that it suggests the RS+ allele (called D in McManus' theory, for "Dextral") to be codominant with the RS− allele (called C for "Chance"). Thus, D homozygous individuals are, according to McManus' theory, 100% right handed. C homozygous carriers have a 50% chance of being left handed. While CD carriers have 25% chance of being left handed. Both theories fit the existing epidemiological and inheritance data for this trait showing that approximately 10% of humans are left handed, that 26% of individuals with two left-handed parents are also left handed while only 20% of those with one left-handed parent and 10% of those with two right-handed parents are left handed. These theories are also consistent with large genetic investigations in twins showing that approximately 25% of the variance in handedness is accounted for by genetic variation (Medland et al. 2009), but not all studies support this view (Vuoksimaa et al. 2009). In this context other possible origins of handedness, such as early developmental abnormalities or trauma (Coren and Halpern 1991), or prenatal hormonal variation (Geschwind and Galaburda 1985), may make some contribution to handedness variability but their influence is uncertain.

There is good evidence showing that variation in handedness is related to some anatomical (Anstey et al. 2004; Yildirim et al. 2006; Manning and Peters 2009) and behavioral (Cherbuin and Brinkman 2006) measures. In addition, the fact that handedness/laterality is also detectable in animals (Annett 2006) and therefore has an origin that can likely be traced back in millions of years (Corballis 2009) suggests that it is not a recent evolutionary effect and that behavioral laterality and left handedness must provide some advantage in order to be preserved through selective processes. In support of this notion, left-handed individuals appear to be overrepresented in professional musicians and other artistic professions (McManus 2002; Kopiez et al. 2009), have a slight advantage in some physical activities (Hagemann 2009), have somewhat better mathematical abilities, and have been found to have lower rates of arthritis and ulcers (McManus and Wysocki 2005).

However, there is also substantial evidence showing that left handedness might be associated with important developmental and health differences. For instance, increased prevalence of certain health problems in left-handed individuals has been reported for cardiovascular disease, high blood pressure, thyroid disorder, motor coordination disorder, dyslexia, asthma, multiple sclerosis, type 1 diabetes (Bryden et al. 2005; Cairney et al. 2008; Preti et al. 2008; Gardener et al. 2009), but decreased prevalence in left handedness has also been found in type 2 diabetes (Hermans et al. 2009) and other studies have failed to replicate some of these effects. Some evidence suggesting an association between handedness and mental illness is also available (Somers et al. 2009; Kalinin et al. 2010).

In contrast, associations between cognitive performance and handedness have been investigated in large cohorts and have shown only small or no effect (Hardyck et al. 1976; McManus and Mascie–Taylor 1983). A recent study that investigated cognitive decline in a prospective study of ageing also found no effect of handedness (Van der Elst et al. 2008) but a cross-sectional investigation of 1669 individuals aged 55–95 years found that poor cognitive function was more likely in nonright-handed individuals (Siengthai et al. 2008). Adding further complexity, Doody et al. (1999) showed that age of onset of Alzheimer's disease occurred earlier in left-handed individuals but was followed by a slower rate of decline. These findings were consistent with those of another study (Seltzer et al. 1984) demonstrating that left-handed individuals were overrepresented in early-onset AD, but partly contradicted another that found a reduced frequency of left handedness in late-onset dementia and no association between severity of impairment and strength of handedness (de Leon et al. 1986).

It has been argued that these somewhat inconsistent findings are likely due to the way handedness is assessed and classified with most investigations using an oversimplified binary measure despite available evidence suggesting important differences between consistent handedness (left or right) and inconsistent and mixed handedness (Corballis 2009). A more sensitive way of assessing handedness involves measuring hand preference using a typical questionnaire (e.g., Edinburgh Inventory) that yields a handedness score (usually ranging from -1 to $+1$) but instead of reducing the measure to a binary variable, it is decomposed into direction (left/right) and strength (absolute value of the handedness score) components that are used in analyses together thus not losing any variance of the original measure. Studies which have considered not only the direction but also the strength of handedness have found that mixed-handed but not strongly left-handed individuals had lower cognitive measures (Peters et al. 2006; Corballis et al. 2008; Rodriguez et al. 2010), scored higher on schizotipic scales (Annett and Moran 2006; Somers et al. 2009), had poorer physical (Bryden et al. 2005) and mental health (Rodriguez et al. 2010), and had higher rates of asthma (Peters et al. 2006), ADHD (Peters et al. 2006; Rodriguez et al. 2010), and dyslexia (Peters et al. 2006). However, de Leon and colleagues (1986) found no association between severity of impairment and strength of handedness in late-onset dementia. Recently, Luders and colleagues (2010) also showed that mixed handedness, but not left handedness per se, was associated with corpus callosum thickness. In addition, Leask and Crow (2006) found that when behavioral as opposed to self-reported

handedness measures were considered, peak performance occurred somewhere between mixed handedness and strong handedness. Thus, it is possible that genetic or early developmental differences in left-handed but more likely in mixed-handed individuals might be associated with life-long influences that may have implications for healthy ageing.

The aim of this study was to investigate whether atrophy of two cerebral structures that are known to be sensitive to genetic and environmental factors, the hippocampus and amygdala, was associated with handedness. These cerebral structures were chosen because they are very sensitive to physiological stress and known to be influenced by pathological processes implicated in cognitive ageing and dementia and therefore may index well small interindividual variations in health and biology. For example, hippocampal and amygdalar volumes are known to be influenced by APOE genotype (Cherbuin et al. 2007), testosterone exposure in utero (Kallai et al. 2005), developmental and life-long stressors (Miller and O'Callaghan 2005; McEwen 2008), anxiety and depression symptomatology (Frodl et al. 2008), cardiovascular disease and diabetes (Anan et al. 2010; Rauramaa et al. 2010), and financial hardship in midlife (Butterworth et al. 2011). These structures are also known to be strongly associated with cognitive ageing and dementia.

To avoid major confounds associated with cross-sectional studies, we investigated the association between both direction and strength of handedness and prospective hippocampal and amygdalar atrophy in a narrow-age cohort of individuals participating in a large longitudinal study of ageing. Given the inconsistent findings reviewed above, it is difficult to present definite predictions. However, since it appears that mixed or weak handedness is most consistently associated with developmental disorders and adverse health outcomes, we expect that weaker handedness measures will be associated with greater hippocampal and amygdalar atrophy.

Methods

Study population

The design of the Personality and Total Health (PATH) Through Life study has been described elsewhere (Jorm et al. 2004) as has the Magnetic Resonance Imaging (MRI) substudy (Anstey et al. 2004). Briefly, participants who were residents of the city of Canberra and the adjacent town of Queanbeyan, Australia, were recruited randomly through the electoral roll to participate in a study interested in the risk and protective factors for normal ageing, dementia, and other neuropsychiatric disorders. Enrolment to vote is compulsory for Australian citizens. Participants were recruited in three age cohorts 20–24, 40–44, 60–64 and are to be followed every 4 years, over a total period of 20 years. This study is concerned with data collected for the older cohort at waves 1 and 2 between 2001 and 2005. Of the 2551 participants included in this sample at wave 1, a subsample of 471 individuals was offered and accepted a structural MRI scan. Of those 431 underwent an MRI scan at wave 2 and after excluding participants with neurological disorders, MRI images of poor quality, and missing handedness data, 327 participants were available for longitudinal analyses. The study was approved by the Australian National University Ethics Committee and all participants provided written informed consent.

Sociodemographic and health measures

Total years of education, heart problems (e.g., atrial fibrillation, angina, etc.), diabetes, stroke, anxiety and depression medication, and smoking were assessed by self-report. Hypertension was assessed using objective blood pressure measures (diastolic > 90; systolic > 140 on average of two seated measures) and self-reported antihypertensive medication use. APOE*E4 genotype was determined from DNA collected by cheek swab.

Handedness measure

Handedness was assessed by the Edinburgh Handedness Inventory (EHI; Oldfield 1971), a 10-item questionnaire surveying which hand is used to perform discrete tasks (e.g., "Which hand do you use to hold a spoon?" and using a five-point scale (-2 always left, -1 mostly left, 0 either, $+1$ mostly right, $+2$ always right). A global handedness score ranging from -1 (extremely left handed) to $+1$ (extremely right handed) was computed by averaging all responses and dividing by two. This score was then used to produce two additional measures of handedness direction ($< 0 =$ left; $> 0 =$ right) and handedness strength (absolute value of the handedness score ranging from 0 to 1).

MRI scan acquisition

All participants were imaged with a 1.5 Tesla Philips Gyroscan ACS-NT scanner (Philips Medical Systems, Best, The Netherlands) for T1-weighted 3D structural MRI. The T1-weighted MRI was acquired in coronal orientation using a fast-field echo sequence (FFE) with the following parameters: Wave 1 repetition time (TR)/echo time (TE) = 28.05/2.64 ms, flip angle = 30°, matrix size = 256 × 256, field of view (FOV) = 260 × 260 mm, slice thickness = 2.0 mm, and mid-slice to mid-slice distance = 1.0 mm, yielding overcontiguous coronal slices; Wave 2 TR = 8.93 ms, TE = 3.57 ms, flip angle of 8°, matrix size = 256 × 256, slices 160, and FOV 256 × 256 mm. Slices were contiguous with slice thickness of 1.5 mm.

Image analysis

Hippocampal and amygdalar volumes were determined by manually tracing the periphery of the Region of Interest (ROI) on each slice of a T1-weighted scan in coronal orientation using Analyze 5.0 (Brain Imaging Resource, Mayo

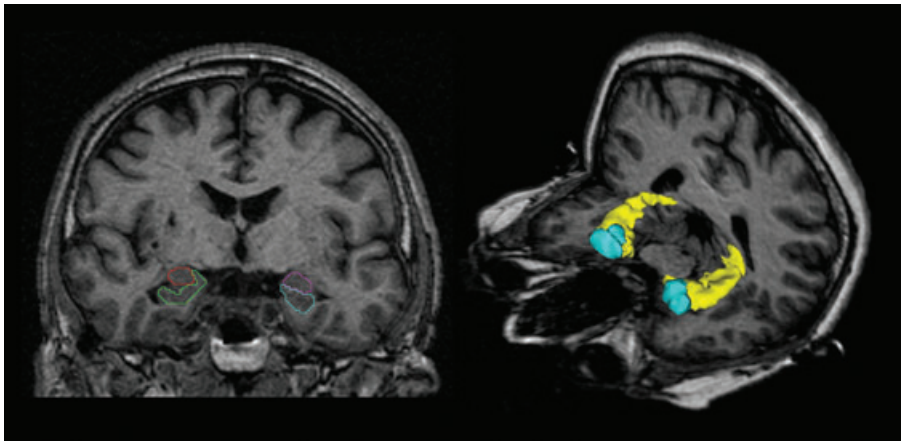

Figure 1. Left: Manual tracings from the analyze package of the left and right hippocampi (green and blue) and of the left and right amygdala (red and purple). Right: 3D model of the hippocampus (yellow) and of the amygdala (blue) rendered in Slicer (slicer.org).

Clinic, Rochester, MI; Fig. 1) by the same experienced tracers. The outlining of the hippocampus and amygdala always proceeded from anterior to posterior and was traced according to the protocol outlined by Watson and colleagues (Watson et al. 1997) with a modification suggested by Brierly et al. (2002). Volume estimations were repeated on 10 randomly selected scans and interclass correlations between raters ranged from 0.948 to 0.989 and 0.981 to 0.993 for the right and left hippocampus, and from 0.975 to 0.989 and 0.995 to 0.996 for the right and left amygdala, respectively (averaged 0.982 and 0.996) (Maller et al. 2007). Intracranial volume (ICV) was computed with the Freesurfer/FSL package (http://surfer.nmr.mgh.harvard.edu/; Fischl et al. 2002, 2004) for wave 1 and wave 2 images.

Statistical analysis

Descriptive analyses were conducted using chi-square for categorical data and *t*-tests to compare groups on continuous variables. Associations between direction and strength of handedness and hippocampal and amygdalar volume and atrophy were investigated using hierarchical multiple regression analyses while controlling for sex, age (years), education (years), ICV (liters), APOE*E4 genotype (E4 carrier vs. noncarrier), hypertension (binary), heart problems (binary), diabetes (binary), stroke (binary), anxiety and depression medication (binary), and smoking (binary) (covariates were assessed at wave 1). Covariates were entered in the first model while hippocampal or amygdalar volumes were entered in the second model. Hippocampal and amygdalar atrophy was assessed by controlling for wave 1 volume in the analyses (i.e., including wave 1 volume as covariate in the first model). In addition, because the image acquisitions were different between waves, the difference in ICV between wave 1 and wave 2 was also controlled for by entering it as a covariate in the first model. Differences in putative associations between strength of handedness and cerebral structures in left- and right-handed individuals were assessed by testing an interaction factor between these variables in the analyses. Interactions between strength and direction of handedness and sex were also tested by entering a cross-product term in a third model. Alpha was set at 0.05.

Results

Participants were on average 62.6 years (range 60–66; SD = 1.41) at wave 1 with a mean follow-up of 4.02 years. Average atrophy per annum was 2.56% for the left and 1.58% for the right hippocampus, while an annual increase in volume of 0.50% for the left and 2.20% was observed for the amygdala. Table 1 presents the demographic and brain variables of the left- and right-handed participants. Of the 327 participants included in the analyses, 25 were left handed (7.6%). Left- and Right-handed individuals did not differ in age, level of education, race, APOE*E4 genotype, hypertension, heart problems, stroke, smoking, or ICV, but left-handed individuals were less likely to be female, were less strongly handed, and were more likely to have diabetes.

ICVs at wave 1 and wave 2 were found to be different with the wave 2 volume being slightly (2.5%) but significantly smaller, $t(326) = 7.807$, $P < 0.001$. For this reason, analyses below investigating hippocampal and amygdalar atrophy were corrected for both ICV at wave 1 and difference in ICV between wave 1 and wave 2. The possible impact of ICV differences across waves on measures of hippocampal and amygdalar atrophy was also further investigated with correlational analyses (not shown) and showed that the difference in ICV between wave 1 and 2 explained less that 1.5% of the variance in hippocampal and amygdalar atrophy measured with manual tracings.

Table 2 presents results from the second model of the hierarchical linear regression analyses, investigating the

Table 1. Demographic, health, and brain characteristics of left- and right-handed participants.

	Left ($n = 25$)	Right ($n = 302$)	(t/χ)	*P*
Demographic variables				
Female (%)	6 (24.00)	146 (48.44)	5.501	0.019
Age at wave 1, years (SD)	62.52 (1.39)	62.61 (1.41)	−0.293	0.770
Age at wave 2, years (SD)	66.44 (1.36)	66.64 (1.41)	−0.667	0.505
Education, years (SD)	14.30 (2.33)	14.31 (2.62)	−0.013	0.990
Caucasian (%)	24 (96.00)	290 (96.02)	0.000	0.995
Strength of Handedness (SD)	0.63 (0.29)	0.84 (0.18)	−3.652	0.001
Diabetes at wave 1 (%)	5 (20.00)	22 (7.28)	4.928	0.026
Hypertension at wave 1 (SD)	8 (32.00)	68 (22.52)	1.394	0.498
Heart Problems at wave 1 (%)	3 (12.00)	36 (11.92)	0.000	0.991
APOE*E4 genotype (%)	10 (40.00)	80 (26.49)	2.113	0.113
Stroke at wave 1 (%)	2 (8.00)	11 (3.64)	1.148	0.284
Smoker at wave 1 (%)	9 (36.00)	106 (35.09)	0.008	0.928
Brain variables				
ICV w1, liters (SD)	1.63 (0.20)	1.58 (0.20)	1.277	0.203
ICV w2, liters (SD)	1.59 (0.20)	1.54 (0.18)	1.501	0.134
TBV at w1, liters (SD)	1.24 (0.12)	1.22 (0.13)	0.621	0.535
TBV at w2[1], liters (SD)	1.07 (0.10)	1.06 (0.10)	0.280	0.780
Hippocampus w1 Left, mL (SD)	2.90 (0.44)	2.83 (0.43)	0.705	0.482
Hippocampus w1 Right, mL (SD)	2.94 (0.38)	2.89 (0.45)	0.594	0.553
Amygdala w1 Left, mL (SD)	1.20 (0.23)	1.23 (0.25)	−0.644	0.520
Amygdala w1 Right, mL (SD)	1.22 (0.28)	1.20 (0.25)	−0.215	0.830
Hippocampus w2[1] Left, mL (SD)	2.53 (0.42)	2.52 (0.40)	0.175	0.861
Hippocampus w2[1] Right, mL (SD)	2.77 (0.44)	2.67 (0.41)	1.202	0.230
Amygdala w2[1] Left, mL (SD)	1.20 (0.32)	1.22 (0.22)	−0.477	0.633
Amygdala w2[1] Right, mL (SD)	1.29 (0.22)	1.27 (0.23)	0.248	0.804

ICV = intracranial volume; TBV = total brain volume.
[1]Cerebral volumes at wave 2 are adjusted for ICV w1/w2 difference.

association between direction and strength of handedness and hippocampal and amygdalar volume at wave 1 or atrophy over 4 years after controlling for sex, age, education, ICV (wave 1 and wave 1 − wave 2 difference), APOE*E4

Table 2. Handedness predictors (direction and strength of handedness) of hippocampal and amygdalar volume at wave 1 and of atrophy over 4 years.

Predictors	Wave 1 hippocampal volume[1]				Hippocampal atrophy[2]				Wave 1 amygdalar volume[1]				Amygdalar atrophy[2]			
	Left		Right		Left		Right		Left		Right		Left		Right	
	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*
Handedness																
Direction	0.020	0.732	0.020	0.720	−0.003	0.946	−0.057	0.194	0.045	0.407	0.034	0.546	0.014	0.771	−0.010	0.885
Strength	−0.035	0.365	−0.035	0.539	**0.118**	**0.013**	**0.116**	**0.010**	0.037	0.513	−0.012	0.840	−0.018	0.848	**0.105**	**0.040**
	R^2	*P*	R^2	*P*	R^2	*P*	R^2	*P*	R^2	*P*	R^2	*P*	R^2	*P*	R^2	*P*
	(ΔR^2)	(*P*)	(ΔR^2)	(*P*)	(ΔR^2)	(*P*)	(ΔR^2)	(*P*)	(ΔR^2)	(*P*)	(ΔR^2)	(*P*)	(ΔR^2)	(*P*)	(ΔR^2)	(*P*)
Model Fit	0.249	<0.01	0.392	<0.01	0.406	<0.01	0.461	<0.01	0.169	<0.01	0.115	<0.01	0.353	<0.01	0.320	<0.01
	(0.001)	0.787	(0.001)	0.811	(0.012)	0.038	(0.012)	0.031	(0.004)	0.474	(0.001)	0.833	(0.001)	0.915	(.010)	0.113

[1]Controlled for sex, age, education, intracranial volume, APOE*E4 genotype, hypertension, heart problems, diabetes, stroke, anxiety and depression medication, and smoking.
[2]Controlled for sex, age, education, w1 intracranial volume, w1-w2 intracranial volume difference, APOE*E4 genotype, hypertension, heart problems, diabetes, stroke, anxiety and depression medication, smoking, and wave 1 volume; Atrophy in model[2] is assessed by controlling for wave 1 hippocampal or amygdalar volume, therefore a positive association reflects less atrophy. Statistically significant results are presented in bold.

genotype, hypertension, heart problems, diabetes, stroke, and smoking which were entered in a first model (not presented). Delta R^2 values are presented for each analysis and represent the amount of variance in hippocampal or amygdalar volume/atrophy explained by the direction and strength of handedness.

In cross-sectional analyses no association was found between strength or direction of handedness and hippocampal or amygdalar volume at wave 1.

However, significant associations were found between strength of handedness and left and right hippocampal and right amygdala atrophy. This indicates that weaker handedness (mixed handedness) was associated with greater left and right hippocampal atrophy and greater right amygdalar atrophy over 4 years. Handedness measures explained approximately 1–1.2% of the variance in volume/atrophy.

The possibility of a different association between strength of handedness and hippocampal/amygdalar atrophy in left- versus right-handed individuals was not supported by interaction analyses ($P > 0.1$), although a trend was detected for left amygdala atrophy (Beta $= -0.347$, $P = 0.066$), suggesting that somewhat greater atrophy might be associated with left handedness. However, significant interactions were detected between strength of handedness and sex in predicting atrophy in left (Beta $= -0.581$, $P = 0.022$) and right (Beta $= -0.490$, $P = 0.027$) hippocampus, and in left (Beta $= -0.608$, $P = 0.013$) and right (Beta $= -0.645$, $P = 0.009$) amygdala. Follow-up analyses indicated that these effects were due to mixed-handed men showing greater atrophy than females: left (males: Beta $= 0.171$, $P = 0.024$; females: ns) and right (males: Beta $= 0.198$, $P = 0.003$; females: ns) hippocampus and right amygdala (males: Beta $= 0.337$, $P = 0.038$; females: ns), except for the left amygdala where mixed-handed women showed greater atrophy (males: ns; females: Beta $= -0.145$, $P = 0.064$).

Discussion

The main findings of this study were that decreased strength of handedness irrespective of direction (mixed handedness) was associated with increased hippocampal and amygdalar atrophy but not with wave 1 volumes. Direction of handedness was not associated with wave 1 volumes or atrophy. Moreover, interaction analyses suggested that these associations did not differ in the larger right-handed and smaller left-handed groups. These results are important for two reasons. First, they indicate that, consistent with previous reports in younger cohorts, handedness is associated with anatomical differences in older individuals that are likely to be associated with subtle but persistent factors influencing health status. Second, they bring more support to the view that individuals who do not develop a typically strong behavioral laterality differ significantly from consistently left- and right-handed individuals and are at somewhat higher risk of certain disorders and brain abnormalities.

From the present results, it is not possible to deduce whether a genetic, environmental, or traumatic origin is responsible for the effect demonstrated between handedness and hippocampal atrophy or indeed whether another cause might be involved. However, strength of handedness was associated with prospective hippocampal and amygdalar atrophy (not wave 1 volumes) and handedness is known to be very stable throughout the lifespan.

Therefore, these findings suggest that early individual predispositions or exposures that determine handedness may be responsible for late pathophysiological processes associated with risk factors and/or processes implicated in Alzheimer's disease and more broadly cognitive decline.

One major question requiring an answer in this context is what credible mechanisms could explain an association between handedness, a behavioral phenotype, and atrophy of cerebral structures? Some explanations deserving to be further considered include (1) genetic/developmental determinants of handedness predispose to biological differences associated with pathological outcomes (2) early trauma hypothesized to be responsible for decreased handedness is associated with greater cerebral vulnerability (3) behavioral differences in weakly handed individuals are associated with greater exposure to risk factors of cognitive decline and neurodegeneration.

A large amount of available evidence supports the view that handedness preferences develop very early and are linked to cerebral development differences, findings that are more consistent with either genetic causes or trauma in the first trimester of pregnancy (e.g., due to bacterial infections, alcohol exposure) or hormonal influences. For instance, handedness has been shown to be genetically determined to a large extent (Medland et al. 2009), the majority of fetuses suck their right thumb in the womb as early as in the fifteenth gestational week (Hepper et al. 1991), thumb sucking in utero is strongly associated with hand preference 10–12 years later (Hepper et al. 2005) and cerebral asymmetry which is correlated with handedness has been shown to have an important genetic component in twins (Geschwind et al. 2002). Thus, it is possible that a common genetic factor predisposes to mixed handedness as well as to certain anatomical differences that might be associated with a higher long-term disease risk. Interestingly, the size of the left hemisphere appears to be less influenced by genetics than that of the right (Geschwind et al. 2002), which might provide a rationale for one hemisphere being more affected by certain pathological factors such as those observed in the present study. That is, if the effects detected in the present study have genetic origins they may have a greater influence on the hemisphere more genetically determined while the reverse might be true if the origins are environmental.

Moreover, previous research also provides evidence for an association between handedness and anatomy (Chang et al. 1960; Weber et al. 2006). Interestingly, previous research has shown that bifurcation of the common carotid artery was asymmetrical (Smith and Larsen 1979) and, although we are not aware of a demonstrated relationship with other laterality measures, blood velocity in the middle cerebral artery has been shown to differ in an asymmetrical manner between left- and right-handed individuals during hypoxia (Leutin et al. 2004) hinting at the possibility of different vascular vulnerabilities of the left and right hemispheres between handedness groups. Since vascular risks have been clearly demonstrated in dementia and cognitive decline, even a subtle life-long handedness-related influence might provide some insights into findings showing an association between the onset and course of dementia and handedness (Seltzer et al. 1984; de Leon et al. 1986; Doody et al. 1999).

There is limited evidence supporting the view that differences in behavior between left- and right-handed individuals might be associated with higher exposure to noxious environments or traumatic injuries with some notable exceptions. In a population of 2180 13–17 year olds, a greater proportion of left-handed individuals, again without information on handedness strength, presented with permanent incisors injuries (Canakci et al. 2003). While in another sample of 5033 individuals the risk of some bone fractures was found to be higher in left-handed, but most of all, in mixed-handed individuals when compared to right-handers (Luetters et al. 2003). Thus, it may be that behavioral differences in mixed- or nonright-handed individuals expose them to a higher risk of trauma either because their interaction with the world is in some circumstances less adaptive or because it is somewhat more hazardous for a left-handed person to live in a world generally designed for a right-handed population.

It should be pointed out that although more evidence supporting a genetic origin of handedness has been discussed, some of the findings presented so far would also be consistent with early developmental or traumatic causes. Recently, further evidence has emerged implicating prenatal testosterone exposure, first proposed by Geschwind and Galaburda (1985), as a determinant of handedness and cerebral asymmetry. Manning and Peters (2009) found in a large internet-based study surveying 255,116 participants that the ratio between second and fourth digit (2D:4D ratio), an index that has been shown to be associated with testosterone levels in the womb and not associated with adult levels (Honekopp et al. 2007), is also associated with handedness such that lower 2D:4D ratios, indicating high prenatal testosterone, are associated with both left handedness and mixed handedness. Low 2D:4D ratios have also been shown to be related to low grehlin levels, a hormone implicated in hunger modulation (Jurimae et al. 2008), obesity, ADHD (Stevenson et al. 2007), aggressiveness and sensation seeking (Hampson et al. 2008), and maternal smoking during pregnancy (Rizwan et al. 2007). Thus, testosterone exposure in utero may predispose to both left–right handedness biases as well as to other physiological differences with potentially long-lasting effects. Although this hormonal influence appears to be environmental, evidence showing that the 2D:4D ratio is substantially heritable is also available (Voracek 2008) and suggests that 80% of the variance in 2D:4D ratio is genetically determined (Medland and Loehlin 2008). Of particular relevance for the present study Kallai et al. (2005) found that relative size of the left and right hippocampi was correlated with 2D:4D ratio in young healthy women. The possibility that early and life-long hormonal levels modulate neurodegenerative processes is somewhat supported by the present results showing greater hippocampal atrophy in males than in females.

The possibility that early traumatic injuries of the central nervous system might predispose to left handedness or mixed handedness also finds some support in the literature. For instance, a twin study showed that the sibling with lower birth weight was at higher risk of lower IQ but only in the context of left handedness, suggesting an association between prenatal pathological events and handedness (Segal 1989). A recent prospective study following 1714 children before and after birth found that mothers' depressive symptoms and critical life events (including interpersonal loss, financial difficulties, illness, or injury) before birth were associated with mixed handedness, which in turn was associated with a higher risk of language difficulties and ADHD symptoms at age 5 (Rodriguez and Waldenstrom 2008).

Overall, the available evidence suggests that left handedness but particularly mixed handedness is associated with a number of risk factors, most of which have a strong genetic origin, which could lead to smaller hippocampal and amygdalar volumes and greater atrophy in ageing. A link with pathological processes is further strengthened by the fact that mixed handedness was associated with prospective atrophy but not wave 1 volumes in the present investigation.

This study has some limitations but also significant strengths. Although the subsample of individuals used for analyses has been randomly sampled from a larger cohort, itself randomly sampled from the community, it may not be completely representative of the population at large. The proportion of left handedness and mixed handedness is relatively low because it reflects the population prevalence that might have reduced the power of certain analyses and therefore the ability to detect some small effects particularly where interactions are concerned. In contrast, this research was conducted in a large sample that is more representative than many described in the literature and composed of self-selected volunteers, patients, or undergraduate students. More precise indexes were used to assess both strength and direction of handedness and analyses were carefully controlled for a number of sociodemographic and health variables reducing the

likelihood that these results might be due to some unrelated group differences. It should also be noted that while the amount of variance in hippocampal and amygdalar atrophy explained by the handedness measures was relatively small, this fact does not reduce the significance of these findings. Indeed the present investigation only focuses on a 4-year period and is likely obscured by substantial individual variability in other domains. If the effects detected occur over longer periods they would be likely to explain very substantial amounts of variance in hippocampal and amygdalar atrophy.

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