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Structural laterality is associated with cognitive and mood outcomes: An assessment of 105 healthy aged volunteers

M. Esteves[a,b,c], P. Marques[a,b,c], R. Magalhães[a,b,c], T.C. Castanho[a,b,c], J.M. Soares[a,b,c], A. Almeida[a,b,c], N.C. Santos[a,b,c], N. Sousa[a,b,c], H. Leite-Almeida[a,b,c,*]

[a] Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Campus de Gualtar, Braga 4710-057, Portugal
[b] ICVS/3B's - PT Government Associate Laboratory, Braga/Guimarães, Portugal
[c] Clinical Academic Center – Braga, Braga, Portugal

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ABSTRACT

The human brain presents multiple asymmetries that dynamically change throughout life. These phenomena have been associated with cognitive impairments and psychiatric disorders although possible associations with specific patterns of cognitive aging are yet to be determined. We have therefore mapped and quantified morphological asymmetries in a heterogeneous and aged population (65.2 ± 8.0 years old, 52 male and 53 female) to explore potential associations between the asymmetries in specific brain regions and cognitive performance. The sample was characterized in a battery of neuropsychological tests and in terms of brain structural asymmetries using a ROI-based approach. A substantial number of brain areas presented some degree of asymmetry. Such biases survived a stringent statistical correction and were largely confirmed in a voxel-based analysis. In specific brain areas, like the thalamus and insula, asymmetry was correlated with cognition and mood descriptors as the Stroop words/colors test or depressive mood scale, respectively. Curiously in the latter, the association was independent of its left/right direction. Altogether, results reveal that asymmetry is widespread in the aged brain and that area-specific biases (degree and direction) associate with the functional profile of the individual.

Introduction

The human brain is remarkably asymmetrical and gross distortions of brain symmetry like the Yakovlevian (anticlockwise) torque and the petalia have been recognized for decades (Galaburda et al., 1978; Hugdahl, 2011; Rogers, 2014; Sun and Walsh, 2006; Toga and Thompson, 2003). At the volumetric and cytoarchitectural levels, prominent asymmetries have been reported. A classic example is the marked leftward increase of the planum temporale in most individuals (Lyttelton et al., 2009; Takao et al., 2011; Watkins et al., 2001), while more recent subcortical asymmetries such as the leftward asymmetry of the habenula have been described (Ahumada-Galleguillos et al., In press). Left/right side differences in columnar organization (packing) (Chance et al., 2013) as well as in neuronal morphology (Scheibel et al., 1985) – size and dendritic arborization – have also been demonstrated. Dopamine (Glick et al., 1982) and noradrenaline (Oke et al., 1978) abundance is left and rightward lateralized respectively and marked differences in the expression of opioid receptors and respective ligands between the left and right anterior cingulate cortex were recently shown (Watanabe et al., 2015).

Some structural asymmetries seem to have a functional role. For example, the structural leftward imbalance of the planum temporale has been shown to be increased in musicians with perfect pitch (Keenan et al., 2001) and functional leftward asymmetry for language has been extensively described (see Toga and Thompson (2003)) for review). Moreover, a relevant body of literature describes abnormal structural lateralization associated with neuropsychiatric diseases. For example, right/left caudate volume quotient has been correlated with the manifestation of attention deficit and hyperactivity disorder (ADHD)-like symptoms in healthy subjects (Dang et al., 2016) and Eden et al. (2015) have shown an association between left or right prefrontal white matter pathways and reappraisal or trait anxiety, respectively. Brain asymmetries (or its lack) have also been recognized in obsessive-compulsive disorder (OCD) (Peng et al., 2015), autism (Conti et al., 2016; Herbert et al., 2005) and schizophrenia (Miyata et al., 2012; Narr et al., 2001; Park et al., 2013; Sun et al., 2015) - see also for review (Lindell and Hudry, 2013; Oertel-Knochel and Linden, 2011; Ribolsi et al., 2014; Ribolsi et al., 2009) - suggesting that

* Corresponding author at: Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Campus de Gualtar, Braga 4710-057, Portugal.
E-mail address: hugoalmeida@med.uminho.pt (H. Leite-Almeida).

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asymmetry is crucial for (or at least reflects) proper functioning (Concha et al., 2012). Indeed, morphological asymmetries manifest early in development (Concha et al., 2012; Kasprian et al., 2011; Song et al., 2015) and seem to increase throughout life (Plessen et al., 2014; Zhou et al., 2013). However, while age-induced functional asymmetry changes seem to be associated with preservation of cognitive function as shown by models such as HAROLD (Cabeza et al., 2002) or CRUNCH (Reuter-Lorenz and Cappell, 2008), the association between the dynamic nature of structural laterality and the course of emotional and cognitive faculties throughout healthy aging is not entirely understood. In fact, the healthy aged population has not even been characterized in terms of hemispheric structural asymmetries.

We thus hypothesized that the older brain presents a high number of asymmetrical areas, which should be increased in comparison with younger subjects. Moreover, we hypothesized that many of these asymmetries should be relevant for neuropsychological profiles. In order to achieve these goals, we studied structural laterality in a thoroughly characterized and heterogeneous population of aged individuals and correlated these data with cognitive performance and mood classification.

Methods

Ethics statement

This study was performed in accordance with the Declaration of Helsinki (59th amendment) and approved by national and local ethics review boards (Comissão Nacional de Protecção de Dados, Hospital de Braga, Centro Hospitalar do Alto Ave and Unidade Local de Saúde do Alto Minho). All volunteers signed informed consent and all medical and research professionals who had access to participants' identity signed a Statement of Responsibility and Confidentiality.

Subjects

The population from the Switchbox project, a project that aims to study healthy aging in the population of northern Portugal, was used in the present study. Subjects' recruitment was performed in two phases. Initially, a large sample, representative of the older Portuguese population in terms of sex and education, was cognitively characterized [n=1051 after inclusion/exclusion criteria; subjects were randomly selected from the Guimarães and Vizela local area health authority registries (Costa et al., 2013; Santos et al., 2013, 2014)]. Then, in a second-phase, and based on the neurocognitive assessment, 120 subjects were selected from the previous sample in order to provide cognitive profiles of overall good cognitive performance (n = 60) and overall poor performance (n = 60) for further characterization, including magnetic resonance imaging (MRI) screening. Further details regarding formation of the groups are presented as Supplementary data.

Inability to understand the informed consent, participant's choice to withdraw from the study, incapacity and/or inability to attend the MRI session, dementia and/or diagnosed neuropsychiatric and/or neurodegenerative disorder (medical records) were the primary exclusion criteria. Regarding cognitive impairment, adjusted thresholds for the Mini-Mental State Examination (MMSE) test were calculated and applied, accounting for age and/or education (Busch and Chapin, 2008; Grigoletto et al., 1999). Following the MMSE validation for the Portuguese population (Guerreiro et al., 1994) the following thresholds were used: MMSE score < 17 if individual with ≤ 4 years of formal school education and/or ≥ 72 years of age, and MMSE score < 23 otherwise.

From the 120 subjects recruited for the Switchbox project, nine refused to perform the MRI screening in the assessment day, four had brain lesions/pathology detected through the MRI and two presented excessive motion/artifacts. This resulted in a final sample of 105 participants (description in Table 1 and Supplementay Table 1). All volunteers were right-handed.

Table 1
Population characterization. Distribution of the population included in the global analysis and respective cognitive and mood scores.

	Female	Male
Number of subjects	53	52
Age	66.5 ± 7.7 (51 to 82)	63.8 ± 8.1 (51 to 79)
Years of formal education	4.1 ± 2.8	6.7 ± 4.2
SRT-CLTR	14.0 ± 12.3	18.1 ± 12.7
SRT-DR	4.9 ± 3.2	5.8 ± 2.9
SRT-int	2.8 ± 4.4	2.1 ± 2.5
Dforward	7.2 ± 2.0	8.2 ± 2.4
Dbackward	3.8 ± 2.3	5.0 ± 2.7
Stroop-w	56.8 ± 19.8	71.6 ± 20.0
Stroop-c	46.6 ± 13.8	50.5 ± 15.2
Stroop-wc	26.1 ± 9.9	32.1 ± 14.2
FAS	14.7 ± 9.4	21.1 ± 12.8
GDS	13.2 ± 6.3	8.8 ± 6.3

Cognitive and mood assessment

Cognitive and mood evaluation was performed by a team of trained psychologists and all tests have been previously described (Santos et al., 2014). The Selective Reminding Test (SRT) (Buschke et al., 1995) was used as a verbal learning and memory test and evaluated the following components: consistent long term retrieval (CLTR), long term storage, delayed recall (DR) and intrusions. The Digits Span Test (Wechsler, 1997) was used in the forward (dforward) and reverse (dbackward) order as a measure of attention in the first case and working memory/executive function in the second. The Stroop test (Strauss et al., 2006), which is divided into three modules - words (w), colors (c) and words/colors (wc) - assessed selective attention, cognitive flexibility and response inhibition. Verbal fluency was evaluated through the Controlled Oral Word Association F-A-S (FAS) (Lezak et al., 2004) test, while depressive mood was assessed using the Geriatric Depression Scale (GDS) (Yesavage et al., 1982).

Image acquisition

Acquisitions were performed on a clinically approved Siemens MagnetomAvanto 1.5 T (Siemens Medical Solutions, Elangen, Germany) scanner, in Hospital de Braga, using a 12-channel receive-only Siemens head coil. A T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sequence with repetition time (TR)=2730 ms, echo time (TE)=3.5 ms, flip angle=7°, field of view (FoV)=256·256 mm, 176 sagittal slices, with isotropic resolution of 1 mm and no slice-gap was used.

ROI-based volumetric analysis

For the region-of-interest (ROI) based volumetric analysis, the structural data was processed with the semi-automated workflow implemented in FreeSurfer v5.10 (http://surfer.nmr.mgh.harvard.edu/). This pipeline implements a total of 31 processing steps which include the spatial normalization to Talairach standard space, skull stripping, intensity normalization, tessellation of gray matter (GM)-white matter (WM) boundary and segmentation of cortical, subcortical and WM regions. Results obtained with this pipeline were shown to be reliable across sessions, scanner platforms, updates, and field strengths (Jovicich et al., 2009) and were validated against manual segmentations (Fischl et al., 2002). Details regarding the procedures and improvements implemented throughout the years have been described in several publications (Desikan et al., 2006; Destrieux et al., 2010; Fischl et al., 2002). For the present work only volumes