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Trajectories of imaging markers in brain aging: the Rotterdam Study

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ABSTRACT

With aging, the brain undergoes several structural changes. These changes reflect the normal aging process and are therefore not necessarily pathologic. In fact, better understanding of these normal changes is an important cornerstone to also disentangle pathologic changes. Several studies have investigated normal brain aging, both cross-sectional and longitudinal, and focused on a broad range of magnetic resonance imaging (MRI) markers. This study aims to comprise the different aspects in brain aging, by performing a comprehensive longitudinal assessment of brain aging, providing trajectories of volumetric (global and lobar; subcortical and cortical), microstructural, and focal (presence of microbleeds, lacunar or cortical infarcts) brain imaging markers in aging and the sequence in which these markers change in aging. Trajectories were calculated on 10,755 MRI scans that were acquired between 2005 and 2016 among 5286 persons aged 45 years and older from the population-based Rotterdam Study. The average number of MRI scans per participant was 2 scans (ranging from 1 to 4 scans), with a mean interval between MRI scans of 3.3 years (ranging from 0.2 to 9.5 years) and an average follow-up time of 5.2 years (ranging from 0.3 to 9.8 years). We found that trajectories of the different volumetric, microstructural, and focal markers show nonlinear curves, with accelerating change with advancing age. We found earlier acceleration of change in global and lobar volumetric and microstructural markers in men compared with women. For subcortical and cortical volumes, results show a mix of more linear and nonlinear trajectories, either increasing, decreasing, or stable over age for the subcortical and cortical volume and thickness. Differences between men and women are visible in several parcellations; however, the direction of these differences is mixed. The presence of focal markers show a nonlinear increase with age, with men having a higher probability for cortical or lacunar infarcts. The data presented in this study provide insight into the normal aging process in the brain, and its variability.

1. Introduction

The aging brain undergoes various structural changes, which can manifest themselves clinically in corresponding functional changes. Much research has been dedicated to understanding these brain changes because these do not only inform about healthy brain aging, but also provide a reference point against which pathologic changes can be contrasted.

The development of noninvasive imaging techniques has fueled research into the aging brain in healthy individuals. Since magnetic resonance imaging (MRI) was first introduced in biomedical research in the 1980s, several pioneers performed small studies using this novel technique to assess macrostructural brain changes in aging (Gur et al., 1991; Jernigan et al., 1990, 1991; Krishnan et al., 1990; Pfefferbaum et al., 1994; Sullivan et al., 1995). After approximately one decade, large cross-sectional studies and population-based studies followed to inform about, for example, sex differences and brain changes in a large sample of healthy volunteers, instead of specific control subjects (Coffey et al., 1998; Good et al., 2001; Mu et al., 1999). Simultaneous developments in MRI scanners and software increased the accuracy of structural (volumetric)

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measurements and enabled measuring microstructural (white matter organization) changes in aging (Coupe et al., 2017; Cox et al., 2016; de Groot et al., 2015; Lebel et al., 2012; Sullivan et al., 2001; van Velsen et al., 2013; Vermeer et al., 2002). In the last 15 years, more and more longitudinal studies have been performed to estimate the rate of brain changes in aging or investigating possible causes and effects of these changes (Barrick et al., 2010; Discroll, 2009; de Groot et al., 2016; Du, 2006; Fjell et al., 2013, 2015; Fraser et al., 2015; Narvacan et al., 2017; Pfefferbaum et al., 2013; Raz et al., 2005, 2010; Sexton et al., 2014; Storsve et al., 2014; Sullivan et al., 2010). Overall, these studies show that the vulnerability of the brain to aging is heterogeneous. Furthermore, some studies show sex differences in the effect of age on the imaging markers (Fjell et al., 2015; Narvacan et al., 2017; Pfefferbaum et al., 2013; Raz et al., 2005), whereas others do not (Fjell et al., 2015; Raz et al., 2005).

Against the background, we aimed to comprise these different aspects in brain aging, by performing a comprehensive longitudinal assessment of brain aging in a middle- and old-aged population. We examined trajectories of volumetric, microstructural, and focal MRI markers in aging across a wide age range (45–95 years) in men and women based on a large prospective population-based cohort study with over 10,000 MRI scans. Furthermore, we analyzed the sequence in which MRI markers change in aging, so as to provide an overview of the concurrency of the changing imaging markers.

2. Methods and materials

2.1. Study population

This study is embedded within the Rotterdam Study, an ongoing prospective population-based study designed to investigate causes and consequences of age-related diseases. The design of the Rotterdam Study has been described previously (Ikram et al., 2017). Since 2005, brain MRI was implemented in the core Rotterdam Study protocol, and participants are invited every 3–4 years for repeat imaging. In Fig. 1, a flowchart of the inclusion of the MRI scans is shown. In this study, all available MRI scans from the Rotterdam Study that were acquired since August 2005 (date of installment of the MRI scanner in the research center) were included (n = 12,023 scans). Scans from participants with dementia or Parkinson's disease that were performed after clinical diagnosis were excluded (n = 110 MRI scans from 94 participants). Scans from participants with a symptomatic stroke that were performed after the event were excluded (n = 385 scans from 235 participants). Furthermore, MRI scans with incomplete acquisition, scans with artifacts hampering automated processing, unreliable tissue segmentation (or unreliable intracranial volume segmentation in case for the focal marker analysis), and incomplete ratings of microbleeds, cortical, and lacunar infarcts were excluded (volumetric and

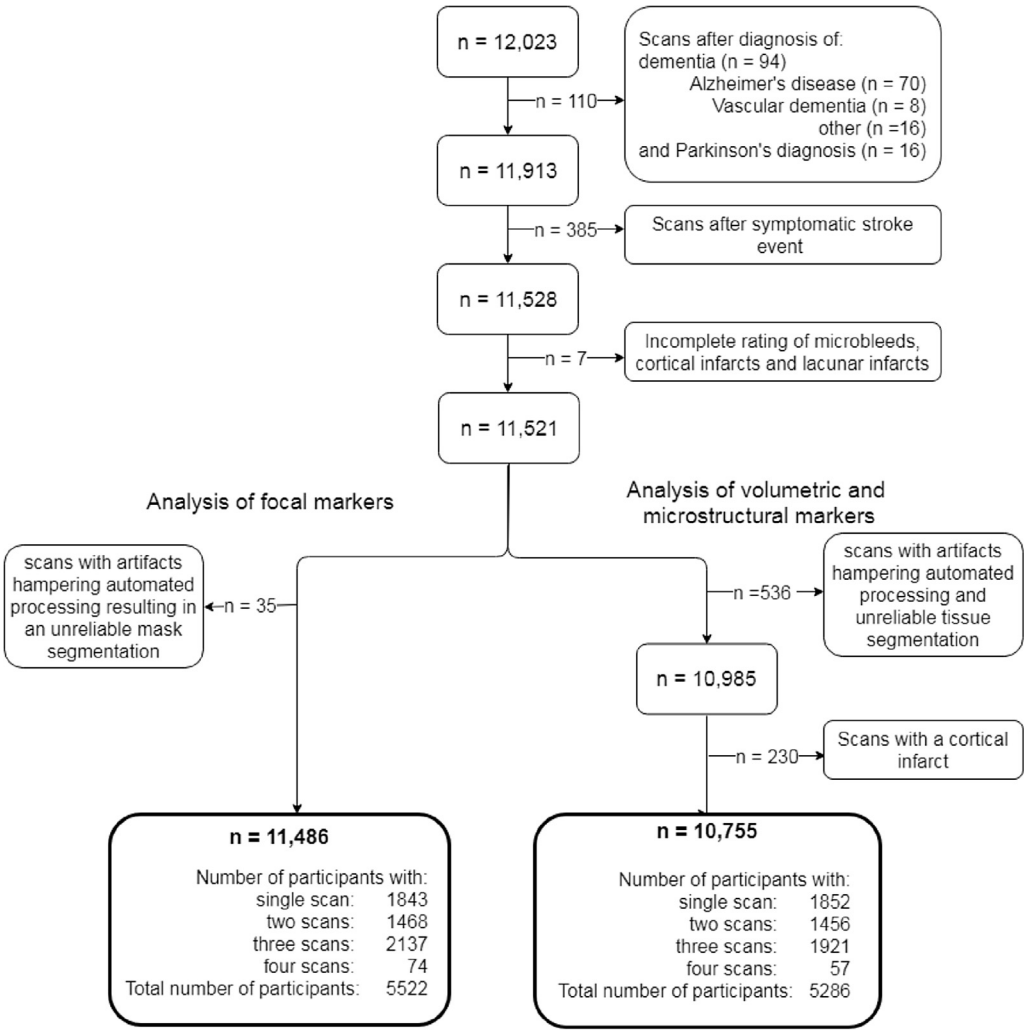

Fig. 1. A flowchart of the inclusion of MRI scans for both the analysis of volumetric and microstructural markers and the analysis of focal markers is shown. Abbreviation: MRI, magnetic resonance imaging.