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Brief communication

Cross-sectional versus longitudinal estimates of age-related changes in the adult brain: overlaps and discrepancies

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ABSTRACT

The healthy adult brain undergoes tissue volume decline with age, but contradictory findings abound regarding rate of change. To identify a source of this discrepancy, we present contrasting statistical approaches to estimate hippocampal volume change with age based on 200 longitudinally-acquired magnetic resonance imaging in 70 healthy adults, age 20–70 years, who had 2–5 magnetic resonance imaging collected over 6 months to 8 years. Linear mixed-effects modeling using volume trajectories over age for each subject revealed significantly negative slopes with aging after a linear decline with a suggestion of acceleration in older individuals. By contrast, general linear modeling using either the first observation only of each subject or all observations treated independently (thereby disregarding trajectories) indicated no significant correlation between volume and age. Entering a quadratic term into the linear model yielded a biologically plausible function that was not supported by longitudinal analysis. The results underscore the importance of analyses that incorporate the trajectory of individuals in the study of brain aging.

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1. Introduction

Heterochronicity in growth and aging trajectories of regional brain volumes has been firmly established with quantitative neuroimaging (e.g., Abe et al., 2008; Giedd et al., 2010; Jernigan et al., 2001; Pfefferbaum et al., 1994; Raz and Rodrigue, 2006; Walhovd et al., 2011). Age-related effects across the adult span have shown areas especially vulnerable to aging, including prefrontal cortex and cerebellar hemispheres and those relatively resistant to aging, including motor, sensory, occipital cortices, corpus callosum, and ventral pons (e.g.,Good et al., 2001; Jernigan et al., 2001; Pfefferbaum et al., 2013; Raz and Rodrigue, 2006; Raz et al., 2005; Walhovd et al., 2011). These observations have been based largely on "cross-sectional" studies, that is, data from healthy individuals of different ages examined once each, with the assumption that resulting age regressions reflect longitudinal change.

Studies across adult ages that have a longitudinal component (i.e., >1 observation per subject at different ages, typically deemed "longitudinal" studies) have confirmed many but not all assumptions about brain development and aging derived from "cross-sectional" studies on the pattern of regional cortical and allocortical age-related effects (Fjell et al., 2010; Pfefferbaum et al., 2013; Raz et al., 2010). The effects of age on hippocampal volume have been inconsistent, with some cross-sectional reports of no age-related declines in men or women (Du et al., 2006; Good et al., 2001; Liu et al., 2003; Sullivan et al., 1995, 2005) and little evidence for heritability of hippocampal volume in old age (Sullivan et al., 2001), whereas other cross-sectional studies report significant age-related hippocampal volume decline (Allen et al., 2005; Greenberg et al., 2008; Jernigan et al., 2001; Lupien et al., 2007; Raz et al., 2004; Walhovd et al., 2011). By contrast, longitudinal studies provide more consistent evidence for untoward effects of aging on hippocampal volume, showing linear (Driscoll et al., 2009; Du et al., 2006) or nonlinear, late-life accelerated decline (Fjell et al., 2013; Pfefferbaum et al., 2013; Raz et al., 2010) (cf., Jernigan and Gamst, 2005). Thus, the extent to which assumptions about change derived from data collected with cross-sectional designs reflects true longitudinal measurement remains controversial (cf., Lindenberger, et al., 2011; Rabbitt, 2011; Raz and Lindenberger, 2011; Salthouse, 2011a).

Practical considerations (i.e., the life span of subjects and investigators) mandate that longitudinal studies of the adult age range comprise asynchronous age observations (i.e., subjects of

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different ages entered into the data set) and heterogeneous observation intervals across subjects. This results in data collected over relatively short time series at different ages in subjects' lives. Thus, even longitudinal studies of normal aging are, in reality, a hybrid of cross-sectional and longitudinal observations. Therefore, analyses using individual trajectories may be the most desirable approach, allowing for both inferences about the normal aging process and interactions between aging trajectories and advancing age, which presents as nonlinear aging.

We present an example of how individual trajectory analysis improves modeling changes with aging despite the substantial heterogeneity in brain structure at any given age. The analyses use hippocampal volumetric data (Fig. 1A) collected longitudinally in healthy adults of different ages (20–70 year old at initial magnetic resonance imaging [MRI]), analyzed 2 ways, demonstrating differences in conclusions to be drawn about age-related effects on regional brain volume depending on the modeling of change employed and the structure measured. First, longitudinal analysis

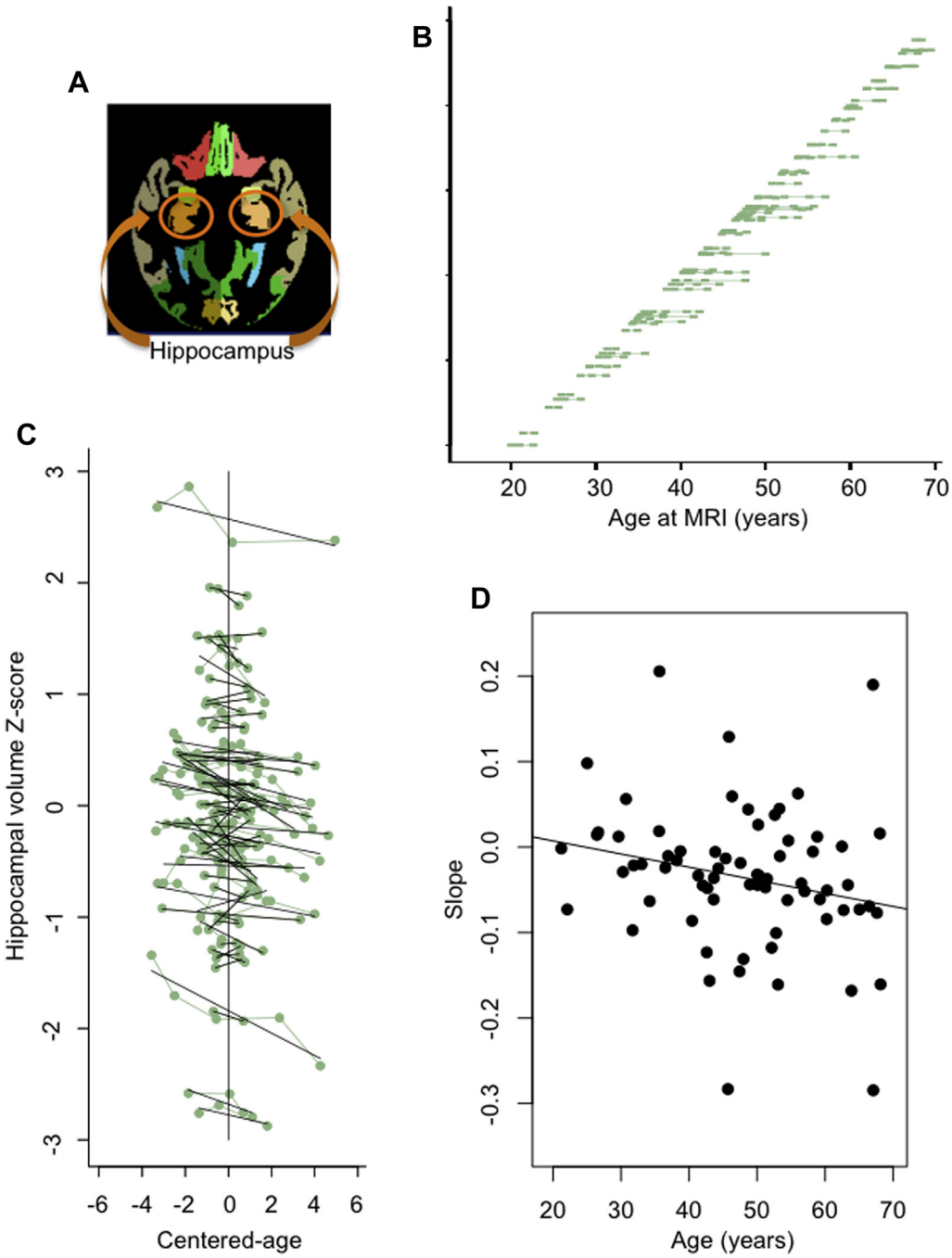

Fig. 1. (A) Axial slice of a parcellated MRI structural image displaying a sample of the hippocampus (orange) used to derive the volume, which was measured over multiple slices. (B) Distribution of ages at each MRI (green square) for each participant. (C) Individual hippocampal z-scores (green dots) and slopes (black lines) plotted as a function of centered-age. For example, for a person who was scanned at ages 40, 45, 47, and 52 years , his mean-age = 46 and his centered-age values after subtracting mean-age were −6, −1, +1, and +6 years. (D) Individual hippocampal slopes plotted as function of each individual's mean age. Abbreviation: MRI, magnetic resonance imaging. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

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