NeuroImage 142 (2016) 293–300

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Selective association between cortical thickness and reference abilities in normal aging

Seonjoo Lee [a,b], Christian Habeck [c], Qolamreza Razlighi [c], Timothy Salthouse [d], Yaakov Stern [c,*]

[a] Division of Biostatistics, New York State Psychiatric Institute, New York, NY, USA
[b] Department of Psychiatry, Columbia University, New York, NY, USA
[c] Division of Cognitive Neuroscience, Department of Neurology, Columbia University, New York, NY, USA
[d] Department of Psychology, University of Virginia, Charlottesville, VA, USA

ARTICLE INFO

Article history:
Received 14 February 2016
Accepted 22 June 2016
Available online 25 June 2016

Keywords:
Cognitive aging
Normal aging
Reference abilities
Principal component analysis
Multivariate multiple regression
L-1 regularization

ABSTRACT

A previous study of reference abilities and cortical thickness reported that association between reference abilities and cortical thickness summarized over large ROIs suppressed was suppressed after controlling for mean cortical thickness and global cognition. In this manuscript, we showed that preserving detailed spatial patterns of cortical thickness can identify reference-ability-specific association besides the association explained by global cognition and mean cortical thickness. We identified associations between cortical thickness and 3 cognitive reference abilities after controlling for mean thickness, global cognition, and linear chronological age: (1) memory, (2) perceptual speed, and (3) vocabulary. Global cognition was correlated with mean overall thickness but also was found to have a regionally specific pattern of associations. Nonlinear associations between cortical thickness and cognition were not observed, neither were nonlinear age effects. Age-by-thickness interactions were also absent. This implies that all thickness–cognition relations and age associations are independent of age and that consequently no age range is inherently special, since brain-behavioral findings are invariant across the whole age range.

Introduction

The association of cerebral atrophy with normal aging (Babakchanian et al., 2012; Chen et al., 2011; Fjell et al., 2009, 2013; Thambisetty et al., 2010; Tisserand et al., 2002) and cognitive decline (Lemaitre et al., 2012; Sanchez-Benavides et al., 2010) has been consistently shown in studies using magnetic resonance imaging (MRI). With the advent of large databases of high-quality data capturing brain structure, precise quantification of structure–function relationships in the brain is possible with unprecedented accuracy and precision. Until recently, structure–function relationships had been subject to prohibitive influences of statistical noise, making the discovery of fine-grained neural substrates of cognition all but impossible: low sample sizes impacted the quality of cognitive instruments and neural measures, which additionally often lacked sufficient spatial resolution. However, with the advent of the software packager FreeSurfer and large databases of high-quality data capturing brain structure, these analyses become more feasible.

Recently, there has been a particular focus on cortical thickness because FreeSurfer enables thickness estimation on the entire cortical ribbon with sub-millimeter resolution, usually at 10,000–100,000 locations ("vertices"). Fine-grained and robust thickness–cognition relationships are the crucial starting point for the enterprise of understanding how brain structure and brain activation give rise to behavior. Once thickness–cognition relationships are demonstrated and understood, one can both ascertain whether these relationships are mediated by brain activation, or whether brain activation contributes to behavior above and beyond the observed thickness–cognition relationship.

Since the relationships between cortical thickness and functional activation are not necessarily local, the best analytic strategy for a multimodal research program is multivariate on conceptual grounds, i.e. we are looking at pattern of correlations between different vertices, and these patterns might ultimately be linked to patterns of functional activation. Multivariate analysis is also the preferred strategy on statistical grounds since our number of variables (= vertices) exceeds the number of observations by 2 orders of magnitude, implying a large degree of redundancy and correlations across subjects between the vertices by necessity. Proceeding vertex-wise in a univariate manner without taking into account this large degree of redundancy would result in overly stringent false-positive corrections with a risk of false-negative findings.

On the side of cognition, a multivariate strategy with the simultaneous consideration of a broad base of cognitive outcomes is also advisable since we are interested in thickness effects that are common to all as well as particular to any individual cognitive outcome. In this paper,

* Corresponding author.
E-mail address: ys11@columbia.edu (Y. Stern).

http://dx.doi.org/10.1016/j.neuroimage.2016.06.041
1053-8119/

we thus engaged in a 2-step procedure: first, we performed principal components analysis on the thickness data to obtain component scores, which are subsequently used in a sparse multivariate regression with 4 cognitive measures as outcomes (episodic memory, fluid reasoning, perceptual speed, and vocabulary). We looked at effects across the whole age range, as well as in age tertiles. We also considered nonlinear effects of age on cognitive outcomes.

The current paper follows from, and can be contrasted with, a recent publication from our group (Salthouse et al., 2015) which examined similar thickness–cognition relations in a subset of the participants in this study. It used a coarser spatial resolution and considered 33 bilateral regions of interest. Remarkably, this investigation yielded few, if any, thickness–cognition relationships that were not accounted for by the general relationship between global cognition and mean thickness. The current paper was a direct extension of these analyses, with the purpose of testing whether finer spatial resolution could uncover more detailed and nuanced thickness–cognition relationships. Therefore, we again included a general, global measure of cognition as a target of prediction, along the 4 specific cognitive abilities in order to ensure that any specific relationships of thickness patterns to cortical thickness were not simply accounted for by the relationship of mean thickness to global cognitive status.

Compared with the many studies investigating the relation of cortical thickness to cognitive performance in healthy and disease populations, our study brings the advantage of coverage across the whole adult lifespan with multivariate cognitive outcomes. The simultaneous consideration of multiple outcomes in a single analytic framework in the current study reduces collinearities and strengthens the specificity of any particular dependencies.

Method

Participants

Market-mailing procedures, flyers, and by word of mouth were used in initial recruitment. In initial telephone screening, participants who met basic inclusion criteria (i.e., right handed, English speaking, no psychiatric or neurological disorders, and normal or corrected-to-normal vision) were further screened in person with structured medical, neurological, psychiatric, and neuropsychological evaluations to ensure that they had no neurological or psychiatric disease or cognitive impairment. Global cognitive functioning was assessed with the Mattis Dementia Rating Scale, on which a score of at least 135 was required for retention in the study. In addition, any performance on tests in the cognitive test battery that was indicative of mild cognitive impairment was grounds for exclusion. More detailed description about this study can be found in Salthouse et al. (2015) and Stern et al. (2014).

The study was approved by the Internal Review Board of the College of Physicians and Surgeons of Columbia University, and after the nature and risks of the study were explained, written informed consent was obtained from all participants prior to study participation. Participants were compensated for their participation in the study.

Cognitive measures

As described in Salthouse et al. (2015), twelve measures were selected from a battery of neuropsychological tests to assess cognitive functioning. Three memory measures were based on sub-scores of the Selective Reminding Task (SRT) (Buschke and Fuld, 1974): the long-term storage sub-score (SRT_LTS), continuous long-term retrieval (SRT_CLRT), and the number of words recalled on the last trial (SRT_Last). For perceptual speed, the Digit Symbol subtest from the Wechsler Adult Intelligence Scale—Revised (Wechsler, 1981), Part A of the Trail Making Test, and the Color Naming component of the Stroop (Golden, 1978; Stroop, 1935) test were chosen. Fluid reasoning ability (GF) was assessed with scores on three different tests: WAIS III Block Design test, WAIS III Letter–Number Sequencing test, and WAIS III Matrix Reasoning test. Vocabulary was assessed with scores on the vocabulary subtest from the WAIS III, the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001), and the American National Adult Reading Test (AMNART) (Grober and Sliwinski, 1991).

MRI acquisition and cortical thickness measures

MRI images were acquired in a 3.0 T Philips Achieva Magnet using a standard quadrature head coil. A T1-weighted scout image was acquired to determine subject position. T1-weighted images of the whole brain were acquired for each subject with an MPRAGE sequence with 180 contiguous 1 mm thick axial slices using the following parameters: TR 6.5 ms, TE 3 ms; flip angle 8°, acquisition matrix 256×256, and 256 mm field of view. A neuroradiologist reviewed anatomical scans, and any with potentially clinically significant findings, such as abnormal neural structure, was removed from the sample prior to the current analysis. In sum, 322 participants were scanned and their MRI images were analyzed. Cortical thickness was measured using the FreeSurfer analysis package (Version 5.1, http://surfer.nmr.mgh.harvard.edu/). In statistical analyses, 144,618 vertices were included after masking out colossal values.

Statistical analyses

Demographics, cognitive, and cortical thickness measures

For the global cognition measure, a principal component analysis of the twelve cognitive measures was performed. Global cognition was quantified as the projection on the first principal component. Each cognition measure was derived as sum of three cognitive measures as defined. The four cognition measures were orthogonalized with global cognition in the statistical analyses.

For cortical thickness measures, the principal component analysis on cortical thickness measures at 144,618 vertices yielded 321 principal components and scores. The first 4 principal components explain 5.4% of total variation in the data, after removing the mean across-subjects vertex pattern.

Demographic information is reported with mean and standard deviation for continuous variables and percent for categorical variables. Spearman's rank-order correlation analyses were performed to test association between demographic variables, mean cortical thickness, and global cognition. Due to the missing values in the cognitive measure and covariates (age and education), $n = 297$ subjects were included in the final analysis. The twelve cognitive measures were standardized by subtracting their means and then dividing by their standard deviations.

Linear and nonlinear association between age and reference abilities

Previous studies (Thambisetty et al., 2010) have reported nonlinear associations between age and cognition. For the five cognitive measures, we examined linear and nonlinear associations in two ways. First, we used nonlinear regression analysis with natural cubic splines (Hastie and Tibshirani, 1990) and tested whether the nonlinear trend significantly improved model fit compared to that of linear model using F-test (Wood, 2013).

Second, we divided the sample to three age groups using age tertiles (33 years and 63 years). We separately fitted linear regression models with cognitive measures as outcomes and age, age group membership, and their interactions as independent variables. Years of education was included as a covariate.

Sparse multivariate multiple regression analyses with covariance estimation

Classical multiple regression models regress a single response on $p \geq 1$ predictors. Multivariate multiple regression is a generalization of