NeuroImage 82 (2013) 284–294

Contents lists available at ScienceDirect

NeuroImage

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

Partial least squares correlation of multivariate cognitive abilities and local brain structure in children and adolescents

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ARTICLE INFO

Article history:
Accepted 21 May 2013
Available online 28 May 2013

Keywords:
Brain morphology
Development
Intelligence
Partial least squares
Multivariate analysis

ABSTRACT

Intelligent behavior is not a one-dimensional phenomenon. Individual differences in human cognitive abilities might be therefore described by a 'cognitive manifold' of intercorrelated tests from partially independent domains of general intelligence and executive functions. However, the relationship between these individual differences and brain morphology is not yet fully understood. Here we take a multivariate approach to analyzing covariations across individuals in two feature spaces: the low-dimensional space of cognitive ability subtests and the high-dimensional space of local gray matter volume obtained from voxel-based morphometry. By exploiting a partial least squares correlation framework in a large sample of 286 healthy children and adolescents, we identify directions of maximum covariance between both spaces in terms of latent variable modeling. We obtain an orthogonal set of latent variables representing commonalities in the brain–behavior system, which emphasize specific neuronal networks involved in cognitive ability differences. We further explore the early lifespan maturation of the covariance between cognitive abilities and local gray matter volume. The dominant latent variable revealed positive weights across widespread gray matter regions (in the brain domain) and the strongest weights for parents' ratings of children's executive function (in the cognitive domain). The obtained latent variables for brain and cognitive abilities exhibited moderate correlations of 0.46–0.6. Moreover, the multivariate modeling revealed indications for a heterochronic formation of the association as a process of brain maturation across different age groups.

Introduction

A major goal of human development research is to identify the functional and structural processes that are predictive of individual cognitive skills (Tau and Peterson, 2010). Magnetic Resonance Imaging (MRI) and computational morphometry have become invaluable tools for *in-vivo* exploration of the underlying changes in healthy brain maturation (Mietchen and Gaser, 2009; Toga and Thompson, 2003). On the one hand, research focused on commonalities shared by children with typical pediatric development has revealed that the general course of brain structure development is distinct in different brain regions and tissue types (Giedd and Rapoport, 2010; Lenroot and Giedd, 2006). Studies observed inverted-U shaped and curvilinear trajectories in gray matter volume (GMV) Gogtay et al., 2004; Lenroot et al., 2007 and cortical thickness (CT) (Shaw, 2008; Shaw et al., 2006; Sowell et al., 2004), and rather continuous increases in white matter volume (WMV) into early adulthood (Ostby et al., 2009; Tamnes et al., 2010c). In addition, trajectories of brain maturation exhibited a substantial sexual dimorphism with delayed peaks in male GMV (Lenroot et al., 2007) and CT (Shaw, 2008) development. On the other hand, there is a growing interest in the individual variability of structural maturational patterns and its relation to differences in cognitive abilities and behavior during adulthood (Deary et al., 2010; Kanai and Rees, 2011). The general intelligence factor, *i.e.* the g-factor, possesses impressive predictive validity for lifespan educational and occupational success, as well as social mobility (Deary, 2012). However, the causes and neurodevelopmental mechanisms underlying individual differences of stable cognitive abilities in adults are still unresolved. Studies exploring general intelligence in relation to brain morphology have been conducted in children and adolescents (Karama et al., 2009, 2011; Lange et al., 2010; Luders et al., 2011; Shaw et al., 2006; Tamnes et al., 2011; Wilke et al., 2003) and younger and middle-aged adults (Haier et al., 2004; Luders et al., 2007, 2008, 2009b; Narr et al., 2007; Tamnes et al., 2011). In addition, recent studies have focused on more specific cognitive abilities and skills in the verbal domain (Porter et al., 2011; Ramsden et al., 2011), working memory (Østby et al., 2011, 2012), and executive functions (Tamnes et al., 2010c). A broad set of cognitive processes contributes to what is commonly referred to as executive functions. Among others, this includes planning, working memory, problem solving and inhibition of responses (Chan et al., 2008). There is neuropsychological and non-clinical evidence for a relation of executive functions to general intelligence (Ackerman et al., 2005; Ardila et al., 2000; Friedman et al., 2008; Salthouse et al., 2003;

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1053-8119/$ – see front matter
http://dx.doi.org/10.1016/j.neuroimage.2013.05.088

Shelton et al., 2009), but as suggested by Friedman et al. (2006) the current intelligence measures do not sufficiently assess these executive control abilities as a contributing factor to 'intelligent behavior'. Thus, in order to capture the complexity of individual differences in cognitive abilities, tests should assess both domains of intelligence and executive function.

Partial least squares framework

Recent studies have emphasized the potential of multivariate analyses for brain development data in general (Bray et al., 2009) and brain maturation in particular (Dosenbach et al., 2010; Hoeft et al., 2011; Lerch et al., 2006; Misaki et al., 2012). The partial least squares (PLS) approach is a class of latent variable algorithms initially originated by Herman Wold (Wold, 1975, 1982) to model associations between two or more blocks of indicators of a system by means of latent variables (Geladi, 1988; Hoeskuldsson, 1988; Wegelin, 2000). PLS has proven to be particularly useful when the number of observations is much smaller than the number of indicators. In addition to applications in psychology, economics, chemometrics and medicine, PLS was successfully introduced to identify associations between multiple behavioral predictors and whole brain activity correlates derived from PET and fMRI (Koutsouleris et al., 2010; Krishnan et al., 2011; McIntosh and Lobaugh, 2004; McIntosh et al., 1996, 2004). There are several advantages of PLS for the purpose of modeling the relationship among local brain structure and multivariate cognitive abilities:

Firstly, the PLS framework naturally extends the classical latent variable approach to cognitive ability tests (Bartholomew, 2004; Carroll, 1993; Jensen, 1998; Spearman, 1904) in a way that directly includes structural properties of brains in the very process of modeling individual differences. In particular, neuroimaging studies that investigate multivariate aspects of individual differences of cognitive abilities (*e.g.* (Barbey et al., in press; Colom et al., 2006, 2007, 2010; Ebisch et al., 2012; Gläscher et al., 2010; Karama et al., 2011)) often apply an analysis procedure with the following two *separate* steps. (A) At first a measurement model of multiple cognitive tests is used to obtain valid estimates of specific cognitive domains or to extract higher order intelligence factors. (B) Afterwards the obtained domain- or factor scores are related to the structural brain data using the general linear model in a mass-univariate manner. Using (A) and (B) basically corresponds to decomposing the unknown multivariate mapping $F: C \rightarrow B$ of the 'cognitive abilities space' to the 'brain structure space' into separate univariate mappings for each voxel/vertex and cognitive domain/factor. By applying PLS we propose a fundamentally different approach that jointly models individual differences in both multivariate spaces in a single generative model of latent variables. Instead of exploring neuronal correlates of *a-priori* fixed cognitive constructs this generalizes the covariance to a multivariate problem with free weightings in both spaces. Moreover, the major difference is that the optimal feature weighting in both spaces is driven by the maximum covariances (see *e.g.* Shawe-Taylor and Cristianini, 2004) instead of maximizing (error-free) variance in factor analysis or latent variable modeling of cognitive tests.

Secondly, the PLS approach is an exploratory method that affords the analysis of structural patterns through the entire brain. PLS overcomes the limitation of the numbers of observed variables in structural equation modeling (SEM) and thus allows the analysis of MR-based images with tens or hundreds of thousands of voxels or vertices without *a-priori* selection of certain ROIs.

Thirdly, PLS models overcome a limitation of mass-univariate approaches by increasing the sensitivity to detect subtle or spatially distributed effects in brain signals (McIntosh and Lobaugh, 2004). Unlike the general linear model (Monti, 2011, for review), PLS explicitly allows modeling effects of numerous strongly collinear or near-linear dependent indicators (Wegelin, 2000), which is especially true for cognitive ability tests (Jensen, 1998).

Fourthly, in contrast to the alternative and very similar canonical correlation analysis (CCA) (Borga et al., 1992, for a unified framework of PLS and CCA), the coefficients derived from PLS modeling were found to be easier to interpret and more stable (Wegelin, 2000). This is mainly because the coefficients in PLS models express the bivariate contribution of each indicator to the latent variables which is in contrast to the mutually dependent coefficients derived from CCA that 'behave' more like multiple linear regression coefficients.

The aim of the current study was to identify latent variables underlying multiple cognitive abilities and local brain structure in a large sample of 286 healthy children and adolescents from the NIH study of normal brain development. By using partial least squares correlation (PLSC) and voxel-based morphometry (VBM) we explored gray matter networks that covaried with a broad set of 19 abilities tests in the domains of intelligence, processing speed, and executive functioning. Finally, we explored age-related maturational differences of the covariance in age groups of younger and older children, and adolescents.

Materials and methods

Modeling cognitive abilities and local brain structure in the PLS framework

Though the PLS framework is much more general we here only focus on the two-block case and use it to jointly analyze individual differences in a set of behavioral predictors and spatial brain variables. We assume the cognitive data and the brain data is represented in two matrices (or blocks) **X** and **Y**, respectively $l \times m$ and $l \times n$. The columns of **X** correspond to cognitive test data, *e.g.* total IQ scores or verbal span. The columns of **Y** contain voxelwise structural brain features after normalization and registration, in particular local gray matter volume maps obtained from VBM. In order to avoid variance differences that may bias the PLS modeling steps, we assume the columns of **X** and **Y** to be standardized features, *e.g.* z-scores. The main idea here is that individual differences observed in **X** and **Y** are generated by two latent variables, say ζ and ξ, respectively. In other words, the columns in **X** and **Y** are assumed to be indicators for the *a-priori* unknown variables ζ and ξ which we estimate from the data. Importantly, ζ and ξ are assumed to covary, in order to represent the cross-covariance of the indicators $\mathbf{X}^T\mathbf{Y}$ at the level (of error free) latent variables, which makes PLSC a special case of structural equation modeling (SEM). A graphical path model representation of the above outlined idea is depicted in Fig. 1A. Our goal to identify directions of maximum covariance in the multivariate observations **X** and **Y** can be further formalized:

$$\sigma_1 = Cov(\zeta_1, \xi_1) = \max_{||u||=||v||=1} Cov(\mathbf{Xu}, \mathbf{Yv}). \quad (1)$$

The desired solution for weightings (or often called saliences) **u** and **v** are the first left and right singular vectors of the cross-block covariance matrix $\mathbf{X}^T\mathbf{Y}$. We here applied the SVD approach to implement the criteria (1) that directly calculates the left and right singular vectors of the covariance matrix $\mathbf{X}^T\mathbf{Y}$. Thus, the main results of this paper further exploit the PLS-SVD algorithm. However, the readers particularly interested in other iterative and kernel-based approaches to PLSC are referred to Supplemental material S1. This also includes the comparison of the underlying orthogonality constraints for PLS-SVD and PLS-NIPALS and the similarity of analysis results of particular PLSC implementations in our NIH dataset.

Application to the NIH study of healthy brain development

Sample

We used a subsample of the NIH MRI study of normal brain development available in the NIH MRI Pediatric MRI Data Repository,