



# Quantitative prediction of individual cognitive flexibility using structural MRI

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## Abstract

Cognitive flexibility, a core dimension of executive functions, refers to one's ability to switch between multiple tasks and sets in a quick and flexible manner. However, whether objective neuroimaging can be used to quantitatively predict cognitive flexibility at the individual level remains largely unexplored. High-resolution magnetic resonance imaging data of 100 healthy young participants from the Human Connectome Project (HCP) dataset were used to calculate gray matter volume (GMV). Cognitive flexibility was assessed by the Dimensional Change Card Sort Test (DCCS). Using a multivariate machine learning technique known as relevance vector regression (RVR), we examined the relationship between GMV and cognitive flexibility performance. We found that the application of RVR to GMV allowed quantitative prediction of the DCCS scores with statistically significant accuracy (correlation = 0.41,  $P = 0.0001$ ; mean squared error = 73.35,  $P = 0.0001$ ). Accurate prediction was mainly based on GMV in the temporal regions. In addition, a univariate approach also revealed an inverse association between DCCS scores and GMV in the temporal areas. Our findings provide preliminary support to the development of neuroimaging techniques as a useful means to inform the cognitive assessment of individuals. Furthermore, the significant contribution of temporal regions suggests the prominent role of temporal cortex morphology in individual differences in cognitive flexibility.

**Keywords** Cognitive flexibility · Prediction · Magnetic resonance imaging · Gray matter volume · Relevance vector regression

## Introduction

Executive functions are defined as the ability to monitor and employ effortful control over cognitive processes, emotional responses, and behavioral impulses (Diamond 2013; Lee et al. 2013). Cognitive flexibility, a core dimension of executive functions, refers to one's ability to switch between multiple tasks and sets in a quick and flexible manner (Diamond 2013;

Rende 2000). This ability facilitates multitasking and allows individuals to regulate their thoughts and actions adaptively in response to changing environmental demands. Cognitive flexibility can be assessed by various neuropsychological tools including questionnaire measures (Dennis and Vander Wal 2010; Martin and Rubin 1995) and variants of the experimental task-switching paradigm (Kiesel et al. 2010). Previous studies have demonstrated that greater cognitive flexibility is linked to favorable outcomes throughout the lifespan, such as better reading abilities in children (Engel de Abreu et al. 2014), higher resilience to negative life events and higher levels of creativity in adulthood (Chen et al. 2014; Genet and Siemer 2011), and greater health related quality of life in older people (Davis et al. 2010). On the contrary, there is an expanding body of evidence that cognitive flexibility deficits are associated with diverse neurological and psychiatric disorders, such as Parkinson's disease (Cools et al. 2001; Lange et al. 2016b), amyotrophic lateral sclerosis (Lange et al. 2016a; Lange et al. 2016c), schizophrenia (Morice 1990; Waltz 2017), autism (Leung and Zakzanis 2014; Memari et al. 2013), obsessive-compulsive disorder (Gruner and Pittenger 2017; Vaghi et al. 2017), and depression (Hou et al. 2016; Murphy et al. 2012).

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The methods commonly used to explore the neural correlates of cognitive flexibility are a combination of paradigms that require cognitive flexibility (e.g., task switching, reversal learning and set-shifting) and neuroimaging techniques (e.g., functional magnetic resonance imaging [fMRI], positron emission tomography [PET] and functional Near Infrared Spectroscopy [fNIRS]), primarily focusing on brain regions that are more activated during cognitively demanding conditions as compared to less demanding ones. By means of these methods, prefrontal cortex and striatum have long been found to be implicated in cognitive flexibility (Badre and Wagner 2006; Cools et al. 2002; Cools et al. 2004; Kim et al. 2011; Leber et al. 2008; Li et al. 2017; Rogers et al. 2000; Wang et al. 2017), which may be modulated by acetylcholine and dopamine transmission (O'Reilly 2013; Prado et al. 2017). However, it can be assumed that structural and functional brain organization, which is measured in the absence of an external task, may also have an influence on cognitive flexibility performance. For instance, Muller et al. have revealed that gray matter volume of the right anterior insula correlates positively with cognitive flexibility performance by using voxel-based morphometry (VBM) analysis (Muller et al. 2015). In a diffusion tensor imaging (DTI) study, cognitive flexibility has been shown to depend on white matter microstructure of the basal ganglia (van Schouwenburg et al. 2014). Furthermore, the application of lesion mapping and resting-state functional connectivity methods has motivated an integrative framework for understanding the neural foundations of cognitive flexibility, highlighting the potential role of a distributed network (e.g., default mode network) in the core elements of this ability (Barbey et al. 2013; Vatansever et al. 2016). However, these functional and structural findings were based on group-level statistics, which is of little use in the prediction of cognitive flexibility at the individual level. It remains unclear whether objective brain imaging methods, e.g., structural MRI, could be used to inform the cognitive assessment of individuals.

Currently, multivariate machine learning techniques have been increasingly employed to increase the translational applicability of neuroimaging data (Brammer 2009; Dosenbach et al. 2010). Compared to traditional mass-univariate approaches, this multivariate method has several potential advantages, notably 1) it allows inferences at the individual level rather than the group level and therefore has greater practical applicability; and 2) it takes inter-regional correlations into account and therefore offers increased sensitivity to subtle and spatially distributed differences (Pereira et al. 2009). As such, it provides an ideal framework for predicting individual cognition which involves a distributed network of regions.

Our aims in the current study were two-fold: first, we tested whether the application of a multivariate machine learning technique to high-resolution structural MRI would allow accurate prediction of individual cognitive flexibility in healthy

young adults; second, we explored which brain regions contributed to such prediction.

## Materials and methods

### Participants

One hundred subjects (46 males) were selected from the Human Connectome Project (HCP) “100 Unrelated Subjects” dataset (<http://www.humanconnectome.org>) (Van Essen et al. 2013). These participants are healthy young adults within a restricted age range of 22–36 years, which corresponds to a period after the completion of major neurodevelopment and before the onset of neurodegenerative changes. Individuals with documented history of severe neurodevelopmental disorders (e.g., autism), psychiatric disorders (e.g., schizophrenia or depression), neurologic disorders (e.g., Parkinson’s disease) or physical disorders (e.g., diabetes or high blood pressure) are excluded, but individuals who are smokers, are overweight, or have a history of heavy drinking or recreational drug use without having experienced severe symptoms are included. The full set of inclusion and exclusion criteria is detailed in prior publications (Van Essen et al. 2013; Van Essen et al. 2012). The HCP scanning protocol was approved by the Institutional Review Board of Washington University in St. Louis, MO, USA. Written informed consent was obtained from each participant.

### Cognitive flexibility measurement

Cognitive flexibility was assessed using the Dimensional Change Card Sort Test (DCCS) (Zelazo 2006) in the NIH Toolbox (<http://www.nihtoolbox.org>) (Gershon et al. 2013; Hodes et al. 2013; Weintraub et al. 2013). In this test, there are two target pictures presented varying along two dimensions (e.g., shape and color). Participants are asked to match sets of two test pictures that differ in color to the target pictures according to the relevant dimension for sorting indicated by a cue word (“shape” or “color”) on the screen. During the test, the target dimension regularly changes, which requires cognitive flexibility to adjust one’s sorting strategy. Scoring is based on a combination of accuracy and reaction time. According to the NIH Toolbox national norms, the raw scores were transferred into the age-adjusted scores (CardSort\_AgeAdj), which were utilized in the current study.

### MRI data acquisition and processing

High-resolution structural images were acquired using a HCP-customized Siemens 3.0 T “Connectome Skyra” scanner with a 32-channel head coil. The imaging parameters of structural MRI were as follows: 3D MPRAGE T1-weighted sequence,

repetition time = 2400 ms, echo time = 2.14 ms, inversion time = 1000 ms, flip angle = 8°, field of view = 224 mm × 224 mm, matrix = 320 × 320, 0.7 mm isotropic voxels, and 256 sagittal slices. The total acquisition time for the structural MRI was 7 min and 40 s. Detailed descriptions of the HCP imaging procedures can be found in previous literature (Van Essen et al. 2013; Van Essen et al. 2012).

Voxel-based morphometry (VBM) analysis was performed using the CAT12 toolbox (<http://www.neuro.uni-jena.de/cat>) implemented in the Statistical Parametric Mapping software (SPM12, <http://www.fil.ion.ucl.ac.uk/spm>). First, all the structural T1-weighted images were corrected for bias-field inhomogeneities. Second, these images were segmented into gray matter, white matter and cerebrospinal fluid density maps using the “new-segment” approach (Ashburner and Friston 2005). Third, the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) technique was used to generate a custom, study-specific template (Ashburner 2007). Fourth, each participant’s gray matter density image was warped to the customized template; then the resultant images were affine registered to the Montreal Neurological Institute (MNI) space and resampled to a voxel size of 1 mm × 1 mm × 1 mm. Fifth, the modulation was applied by multiplying the transformed gray matter density maps with the non-linear components of Jacobian determinants, which resulted in the normalized gray matter volume (GMV) maps representing the local native-space gray matter volume after correcting the confounding effect of variance induced by individual whole-brain size. Finally, to make a balance between compensating for registration errors and reserving anatomical details, the GMV images were smoothed with a moderate full-width at half-maximum (FWHM) Gaussian kernel of 6 mm.

### Multivariate RVR analysis

The relationship between the cognitive flexibility and the GMV was investigated using a multivariate machine learning technique known as relevance vector regression (RVR) (Tipping 2001) implemented in Pattern Recognition for Neuroimaging Toolbox (PRoNTo v2.0, <http://www.mlnl.cs.ucl.ac.uk/pronto/>) (Schrouff et al. 2013). The advantage of RVR relative to other multivariate machine learning techniques, such as support vector machine (SVM), is that it allows the quantitative prediction of a variable of interest without the need for a discrete categorical decision. RVR is a sparse kernel learning multivariate regression method set in a fully probabilistic Bayesian framework, where a zero-mean Gaussian prior is introduced over the model weights. These weights are governed by a set of hyperparameters, that is, one for each weight. Then, the training data are used to iteratively estimate the most probable values for these hyperparameters, with sparseness achieved due to the posterior distributions of many of the weights peaking sharply around zero. Those training vectors associated with non-zero

weights are referred to as relevance vectors. By computing the predictive distribution, the optimized posterior distribution of the weights can be used to predict the target value (e.g., CardSort\_AgeAdj score) based on an input vector (e.g., GMV data).

In this study, the input vectors (i.e., the features) were mean centered using the training data and the samples were normalized. The generalizability of the model was estimated via leave-one-out cross validation, which was indexed by the Pearson correlation coefficient and mean squared error (MSE) between actual and predicted CardSort\_AgeAdj scores. Statistical significance of both indices was determined by permutation testing whereby the input-target data were randomly paired and the RVR procedure was repeated 10,000 times. This resulted in a distribution of correlation coefficients (or MSE values) reflecting the null hypothesis that the model did not exceed change. Then, the number of times the permuted correlation value (or MSE value) was greater (or less) than or equal to the true value was divided by 10,000, resulting in a *P*-value for the correlation coefficient (or MSE). It should be noted that the regression map is a spatial representation of the RVR-derived weight vector and values in the map represent the relative contribution of each voxel to the regression function in the context of every other voxel. For ease of visualization, the weight map was thresholded to show voxels with values ≥50% of the maximum weight vector value across all voxels.

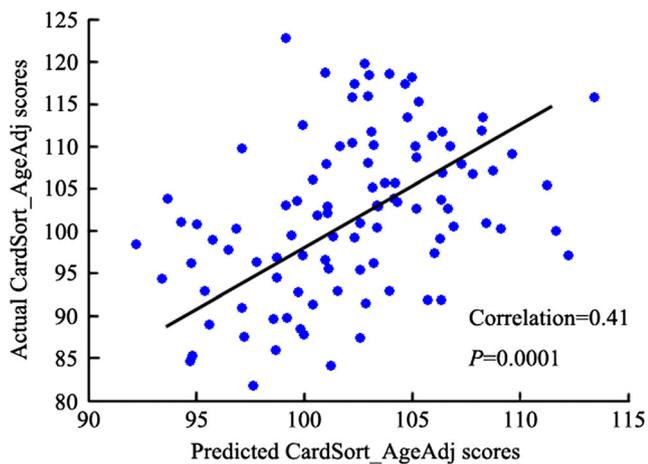
### Univariate SPM analysis

We also used a standard, univariate approach to examine the relationship between the cognitive flexibility and the GMV in a voxel-wise manner within the whole gray matter. A multiple regression model in the SPM12 software was used to identify any voxels in the GMV maps that showed a significant association with the CardSort\_AgeAdj scores. The total intracranial volume was considered as a nuisance variable. Correction for multiple comparisons was performed using the non-stationary cluster-level family-wise error (FWE) method (Hayasaka et al. 2004), resulting in a cluster defining threshold of *P* = 0.001 and a corrected cluster significance of *P* < 0.05. In addition, since permutation test with Threshold-Free Cluster Enhancement (TFCE) has been demonstrated to reach the best balance between family-wise error rate and test-retest replicability (Chen et al. 2018), we validated our results using a permutation-based inference with TFCE.

## Results

### Multivariate RVR analysis

The mean CardSort\_AgeAdj score for the 100 participants was 102.1 ± 9.4 (range of 81.8–122.7). Fig. 1 illustrates that



**Fig. 1** Scatter plot showing the actual CardSort\_AgeAdj score vs. the corresponding predicted score derived from the GMV data using RVR for each subject. Abbreviations: GMV, gray matter volume; RVR, relevance vector regression

the application of RVR to the GMV data allowed quantitative prediction of the CardSort\_AgeAdj scores with statistically significant accuracy (correlation = 0.41,  $P = 0.0001$ ; MSE = 73.35,  $P = 0.0001$ ). The brain regions that contributed the most to the regression function were identified by setting the threshold to  $\geq 50\%$  of the maximum weight vector value. These regions were mainly localized to the temporal cortex including the left anterior middle temporal gyrus (cluster size = 204 voxels, peak MNI coordinates  $x/y/z = -48.5/1.5/-26.5$ , peak weight vector score  $[w_i] = -5.6 \times 10^{-3}$ ), left anterior inferior temporal gyrus (cluster size = 183 voxels, peak MNI coordinates  $x/y/z = -46.5/6.5/-38.5$ ,  $w_i = -5.7 \times 10^{-3}$ ), right anterior middle temporal gyrus (cluster size = 798 voxels, peak MNI coordinates  $x/y/z = 48.5/7.5/-29.5$ ,  $w_i = -8.1 \times 10^{-3}$ ) and right posterior middle temporal gyrus (cluster size = 179 voxels, peak MNI coordinates  $x/y/z = 45.5/-61.5/-0.5$ ,  $w_i = -5.3 \times 10^{-3}$ ) (Fig. 2).

### Univariate SPM analysis

In the voxel-wise whole gray matter analysis, we found significant negative correlations (cluster-level  $P < 0.05$ , FWE corrected; a minimum cluster size of 1024 voxels) between the CardSort\_AgeAdj scores and the GMV in the bilateral middle temporal gyri (left: cluster size = 1544 voxels, peak

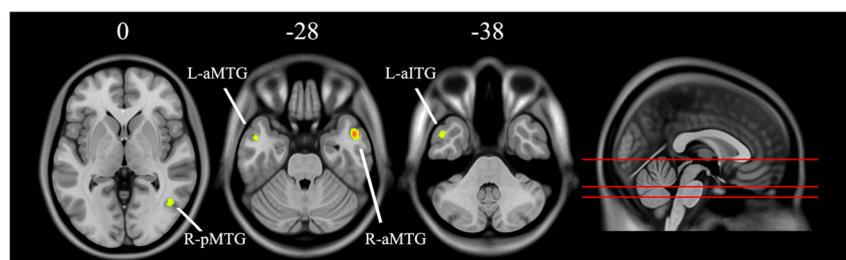
MNI coordinates  $x/y/z = -59.5/-19.5/-7.5$ , peak  $T = -5.1$ , partial correlation coefficient  $[pr] = -0.433$ ,  $P < 0.001$ ; right: cluster size = 4059 voxels, peak MNI coordinates  $x/y/z = 58.5/10.5/-22.5$ , peak  $T = -5.5$ ,  $pr = -0.457$ ,  $P < 0.001$ ) (Fig. 3). In addition, the permutation-based inference with TFCE revealed a similar spatial distribution of brain regions showing significant negative correlations with the CardSort\_AgeAdj scores ( $P < 0.05$ , FWE corrected) (Fig. S1).

### Discussion

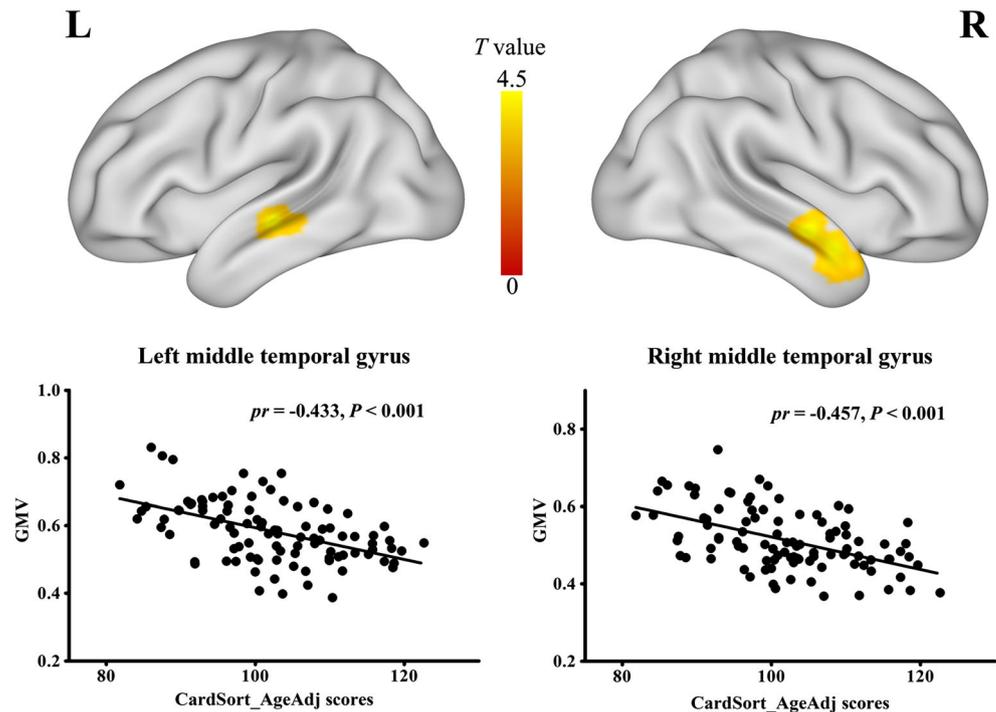
This study demonstrated that the application of RVR to GMV images extracted from high-resolution structural MRI data allows quantitative prediction of individual cognitive flexibility performance with high accuracy, suggesting that objective neuroimaging techniques may inform the cognitive assessment of individuals. In addition, accurate prediction of cognitive flexibility was mainly based on GMV in the temporal regions and an inverse association between them was also revealed by the univariate analysis, indicating the prominent role of temporal cortex morphology in individual differences in cognitive flexibility.

It is somewhat surprising that we did not find any correlations of cognitive flexibility with GMV of the prefrontal cortex and striatum, which seems to contradict previous task-based neuroimaging studies underscoring a crucial role of these regions in cognitive flexibility (Badre and Wagner 2006; Cools et al. 2002; Cools et al. 2004; Kim et al. 2011; Leber et al. 2008; Li et al. 2017; Rogers et al. 2000; Wang et al. 2017). However, such a discrepancy may be a misunderstanding of the present study, because what we did not find is an association between the inter-individual differences in GMV of these regions and inter-individual differences in cognitive flexibility performance. That is, while the prefrontal cortex and striatum are implicated in cognitive flexibility, the GMV extracted from them do not relate to individual performance levels. In addition, it is noteworthy that we focused on the relationship between cognitive flexibility and brain structural parameter, which is considered an inherent trait and independent of states. Thus, based on our design, we cannot draw any conclusions on how brain activity measured during performing a cognitive flexibility task relates to performance. Taken together, our

**Fig. 2** Brain regions with a RVR weight vector value  $\geq 50\%$  of the maximum. Abbreviations: RVR, relevance vector regression; L, left; R, right; aMTG, anterior middle temporal gyrus; aITG, anterior inferior temporal gyrus; pMTG, posterior middle temporal gyrus



**Fig. 3** Brain regions showing significant negative correlations between gray matter volume and cognitive flexibility (cluster-level  $P < 0.05$ , FWE corrected). Scatter plots show the correlations between the mean GMV of the significant clusters and the CardSort\_AgeAdj scores. Abbreviations: L, left; R, right; GMV, gray matter volume;  $pr$ , partial correlation coefficient



findings suggest that when focusing on task-unspecific brain morphology and its relationship with cognitive flexibility performance, it is more the structure of temporal cortex, rather than the prefrontal cortex and striatum, that is related to inter-individual differences.

The temporal cortex is a complex region that involves multiple functions including audition (Kaas and Hackett 1999), vision (Grill-Spector and Malach 2004), language processing (Binney et al. 2010; Hickok and Poeppel 2007; Price 2010; Ralph et al. 2017), memory (Munoz-Lopez et al. 2010; Schacter and Wagner 1999) and social cognition (Green et al. 2010; Olson et al. 2013; Zahn et al. 2009). In the multivariate analysis, the anterior and posterior ventrolateral temporal regions contributed the most to the regression function. The posterior ventrolateral temporal area receives visual input from the occipital cortex and is responsible for combining visual features to form representations of complex shapes and colors (Felleman and Van Essen 1991; Halgren et al. 1999; Kanwisher et al. 1997b). The anterior ventrolateral temporal area is thought to be implicated in multimodal sensory integration, i.e., allowing extraction of the meaning of these shapes and colors (Bell et al. 2009; Kanwisher et al. 1997a; Kriegeskorte et al. 2008). This complex process of sensory information manipulation has been demonstrated to underlie a multitude of cognitive processes (Lambon Ralph 2014; Mesulam 1998; Patterson et al. 2007; Ralph et al. 2017). Therefore, while it is not directly engaged in executive functioning, the functional organization of the anterior and posterior ventrolateral temporal regions may be crucial

for cognitive flexibility. In the univariate analysis, the significant clusters were identified in the middle temporal gyrus. The middle temporal gyrus is unique to human beings and one of its functions is deductive reasoning (Goel et al. 1998), which may partially account for its association with cognitive flexibility performance. Moreover, the negative weight vector score and inverse correlation indicate that smaller volume in these temporal regions is associated with greater cognitive flexibility performance and larger volume associated with poorer performance. This apparently counter-intuitive finding should be interpreted in light of evidence that smaller cortical volume is not necessarily associated with lower number of neurons but might also depend on locally potentiated synaptic pruning, a neurodevelopmental process that has been associated with improved cognitive efficiency (Paus 2005). By seven months gestation, almost all of the neurons destined to comprise the mature cortex have been formed (Goswami 2004). Following birth, brain development initially consists of the growth of synapses, axons and dendrites triggered by synaptogenesis, which leads the synaptic density to reach a maximum. Then, the synaptic density gradually decreases to adult levels through synaptic pruning (Johnson 1997). Thus, the smaller temporal cortex volume may reflect lower synaptic density possibly resulting from a better synaptic pruning, which would be expected to relate to greater cognitive flexibility performance. In contrast, the larger temporal cortex volume may reflect higher synaptic density probably resulting from an insufficient synaptic pruning, which would be

expected to relate to poorer performance. Although our speculation supports synaptic pruning as a major factor, we cannot completely rule out other possibilities. Further studies are needed to reach a definite conclusion.

While the results of our multivariate investigation provide evidence for the implication of the temporal cortex in individual differences in cognitive flexibility, it should be noted that high discriminative power of a region may be driven by (i) a difference in GMV between individuals with low and high scores in that region, and (ii) a difference in the correlation between that region and other regions between individuals with low and high scores. Thus, the four temporal clusters identified in our multivariate analysis should be interpreted as a spatially distributed pattern rather than as independent regions. In addition, it should be noted that these regions were identified using an arbitrary threshold of 50%, and that prediction of cognitive flexibility was to some extent informed by all voxels within the gray matter since no feature selection was employed. In contrast, the mass-univariate correlation analysis considers GMV of each voxel as a spatially independent unit. Although it detected bilateral temporal regions showing a significant association with cognitive flexibility after correction for multiple comparisons, the univariate analysis has limited value in individualized prediction. Therefore, multivariate machine learning techniques may be better suited to the possible development of real-world cognitive prediction tools than mass-univariate methods (Brammer 2009).

There are several limitations that should be mentioned in the present study. First, the HCP sample included only healthy young adults with an age range from 22 to 36 years, which may limit the generalizability of our findings. Future investigations are encouraged to further improve our understanding of individual differences in cognitive flexibility from the lifespan perspective by enrolling a cohort of subjects with a broader age range. Second, while the Dimensional Change Card Sort Test is one of the most frequently used neuropsychological tests for the assessment of cognitive flexibility, it also involves other cognitive domains such as attention, which could have influenced our interpretations to some extent. Third, a combination of GMV and other neuroimaging features derived from modalities such as diffusion weighted imaging and functional MRI might achieve a better and more reliable prediction performance.

In conclusion, our findings provide proof-of-concept that it might be possible to use structural MRI data and multivariate machine learning technique to quantitatively predict individual cognitive flexibility, which supports the development of objective neuroimaging as a useful means to inform the cognitive assessment of individuals. Furthermore, the significant contribution of temporal regions suggests the critical role of temporal cortex morphology in individual differences in cognitive flexibility.

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**Author's contributions** JZ and YY designed the current study and wrote the paper. All of the authors performed the experiments and analyzed the data. All of the authors read and approved the final manuscript.

## Compliance with ethical standards

**Conflict of interest** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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