Modeling Cognitive Processes via Multi-stage Consistent Functional Response Detection

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Abstract. Recent neuroscience research suggested that cognitive processes can be viewed as functional information flows on a complex neural network. However, computational modeling of cognitive processes based on fMRI data has been rarely explored so far due to two key challenges. First, there has been a lack of universal and individualized brain reference system, on which computational modeling of cognitive processes can be performed, integrated, and compared. Second, there has been a lack of ground-truth of cognitive processes. This paper presents a novel framework for computational modeling of working memory processes via a multi-stage consistent functional response detection. We deal with the above two challenges by using a publicly released large-scale cortical landmark system as a universal and individualized brain reference system and as a statistical data integration platform. Specifically, in the first-stage analysis, for each corresponding landmark we measure the consistency of its fMRI BOLD signals from a group of subjects, and the landmarks with high group-wise consistency are found to be highly task-related. In the second stage, the consistency of dynamic functional connection (DFC) time series of each landmark pair from the same group of subjects are measured, and those connections with high consistent patterns are declared as the active interactions during the cognitive task. Here, the group-wise consistent responses inferred from statistical pooling of data from multiple subjects via the universal brain reference system are considered as the benchmark to evaluate the multi-stage framework. Experimental results on working memory task fMRI data revealed that our methods can detect meaningful cognitive processes.

Keywords: cognitive processes, task fMRI, functional response detection.

1 Introduction

Recent neuroscience research has suggested that cognitive processes can be considered as functional information flows on complex neural networks [1-3]. A critical characteristic of cognitive processes is that they are dynamic and hierarchical [7]. With modern advancements of fMRI techniques, researchers are now able to map brain regions involved in the brain's cognitive processes such as working memory with decent spatial and temporal resolutions [4, 5]. However, computational modeling of cognitive processes based on fMRI data has been rarely explored in the literature so far due to at least two key challenges. First, there has been a critical lack of

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universal and individualized brain reference system on which computational modeling of cognitive processes can be performed, integrated, pooled and compared across individuals. The Brodmann brain map and associated atlases have been used for over 100 years in neuroscience, however, the brain regions in Brodmann map at the gyral or sulcal scale are relatively coarse to map and represent fMRI BOLD signals. Second, there is no ground-truth for both cognitive processes and fMRI data. Actually, it has been a longstanding challenge to evaluate results in fMRI-based mapping of brain function and computational modeling of cognitive processes.

In this paper, we present a novel framework for computational modeling of cognitive processes (using working memory as a test-bed) via multi-stage consistent functional response detection. Specifically, we deal with the abovementioned two challenges by using a publicly released large-scale cortical landmark system [6] with 358 common and individualized cortical landmarks, named DICCCOL (Dense Individualized and Common Connectivity-based Cortical Landmarks), as a universal and individualized brain reference system. Experimental results have shown that this DICCCOL brain reference system offers much finer granularity, much better functional homogeneity, and intrinsically-established correspondences across individuals and populations, in comparison with the Brodmann map and atlases [6]. Therefore, the DICCCOL system not only can be used for the computational modeling of dynamic and hierarchical cognitive processes, but also can be used as a statistical data integration platform. As a result, the group-wise consistent functional responses inferred from statistical pooling of data from multiple subjects can be considered as the benchmark to evaluate the multi-stage framework. Given the lack of ground-truth of cognitive processes, group-wise consistency and reproducibility across individuals are probably the desired choice at the current stage.

Specifically, in the first-stage modeling, for each corresponding DICCCOL landmark from a group of subjects, we measure the consistency of its fMRI BOLD signals, and the landmarks with high group-wise consistency are determined as highly task-related ones. These landmarks are thus considered as the first-stage information processing centers. In the second-stage modeling, the consistency of dynamic functional connectivity (DFC) time series of each landmark pair from the same group of subjects are quantitatively measured, and those connections with highly consistent patterns are regarded as the active functional interactions during the cognitive task. The proposed multi-stage consistent response detection framework has been applied on a working memory task-based fMRI dataset [8] to computationally model the dynamic and hierarchical working memory process, and experimental results revealed that our methods can detect meaningful cognitive processes.

2 Materials and Methods

2.1 Overview

The computational framework of our multi-stage fMRI data analysis and modeling based on large-scale cortical landmarks are summarized in Fig.1. First, the structurally and functionally corresponding 358 DICCCOL landmarks are localized and optimized via the methods in [6] for each subject in a group based on DTI data. The DTI images are co-registered with the working memory task-based fMRI data [8] for each subject in order to extract fMRI signals for the cortical landmarks [6]. Second, we calculate the dynamic functional connections (DFC) between each pair of

cortical landmarks, which are used to represent the time-varying functional interaction responses to external block-based stimulus. In general, the consistent response detection framework consists of two stages. In the first stage, we conduct group-wise consistency analysis directly on fMRI BOLD signals of each corresponding DICCCOL landmark from a group of subjects, based on which we determine the first-stage information centers for the working memory cognitive task. In the second stage, we perform group-wise consistent response detection on the DFC time series of corresponding cortical landmark connections across subjects. Based on the results in this stage, we detect active interactions and determine second-stage information processing centers. Then, the landmarks and connections that exhibit either consistent BOLD response or consistent functional connectivity responses are integrated to represent hierarchical working memory cognitive processes, in comparison with traditional activation detection results by group-wise GLM method [5, 12].

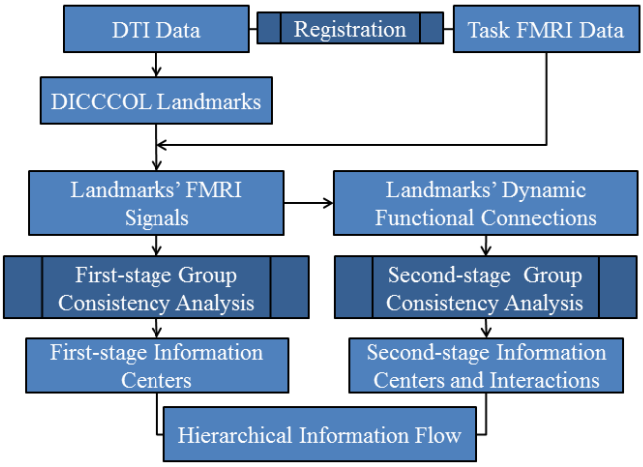


Fig. 1. The pipeline of task-based fMRI data processing, analysis and modeling

2.2 Data Acquisition and Pre-Processing

In a working memory task-based fMRI experiment under IRB approval [8], fMRI images of 19 healthy young adult subjects are scanned on a 3T GE Signa scanner. The acquisition parameters are as follow: fMRI: 64×64 matrix, 4mm slice thickness, 220mm FOV, 30 slices, TR=1.5s, TE=25ms, ASSET=2. Each participant performed the modified version of the OSPAN task (3 block types: OSPAN (30 TRs) with a response (10 TRs), Arithmetic (20 TRs), and Baseline (20 TRs)), while fMRI data was acquired. DTI data was acquired with dimensionality 128×128×60, spatial resolution 2mm×2mm×2mm; parameters are TR 15.5s and TE 89.5ms, with 30 DWI gradient directions and 3 B0 volumes acquired. The DTI data was co-registered to the fMRI space via FSL FLIRT. For fMRI images, the pre-processing pipeline includes motion correction, slice time correction, temporal pre-whitening, spatial smoothing, and global drift removal. For DTI data, pre-processing includes skull removal, motion correction and eddy current correction. The brain tissue segmentations were performed on the DTI-derived images via the similar approaches in [9]. The fiber

tracking was performed using the MEDINRIA package. For each subject, the 358 DICCCOL landmarks with structural correspondences are localized and optimized on white matter cortical surface via the computational framework in [6].

2.3 FMRI Signal Extraction for Each Landmark

DTI images of each subject were first registered into the fMRI space via FSL FLIRT [10]. As DICCCOL landmarks were localized and optimized on the DTI white surfaces, which were reconstructed from DTI-derived tissue maps, we first translate the landmark locations into voxels of DTI tissue maps. With the registration of DTI and fMRI data, we then locate the landmarks on fMRI images and extract corresponding fMRI signal for each landmark. As our work majorly focuses on the relative fluctuation of fMRI signals and their inter-relationship, we normalize each extracted signal $S = [s_1, s_2, \ldots\ldots, s_n]$ before all the analyses as: $S_{norm} = \frac{S - \frac{\sum_{i=1}^{n} s_i}{n}}{\sigma_S}$ (1)

2.4 Cortical Landmarks' Dynamic Functional Connections

A sliding window method was applied to measure the temporally dynamic functional interaction of two cortical landmarks based on their fMRI signals, and the generated time series is defined as the dynamic functional connection (DFC) of these two landmarks, as illustrated in Fig.2. Specifically, given an fMRI signal with the total length of T (units in fMRI image volume), and the sliding window with the width of t_w, at each time point t_n, we extracted a signal window with length t_w centered at t_n (Fig.2(b)). With two signal windows obtained from different fMRI signals of two cortical landmarks, we calculated the Pearson's correlation between them and defined it as the dynamic functional connection at t_n (Fig.2(b)). Note that for the first and last few time points in the fMRI BOLD signal, the window length is shortened to calculate the correlation. After sliding over all the time points, the resulted DFC time series have the same length of T as the original fMRI signals. Thus, we can measure the functional interactions among cortical landmarks through DFC time series signals, as illustrated at the bottom of Fig.2(b).

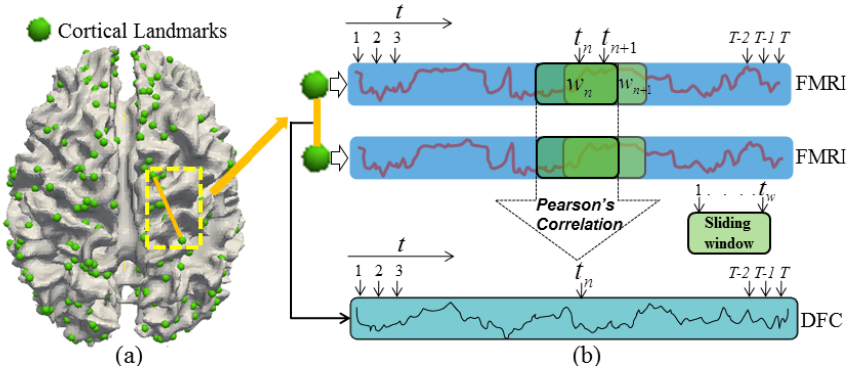


Fig. 2. DFC calculation for an example landmark pair. (a) Green spheres are 358 DICCCOL landmarks. An exemplar connection of landmark pair is illustrated as a yellow line in the yellow dashed frame. (b) A sliding window approach is applied on two fMRI signals of a landmark pair and the DFC is then calculated.

2.5 Multi-stage Consistent Functional Response Detection

To measure a set of time series signals' consistency, e.g., a group of fMRI BOLD signals for the same cortical landmark in 19 subjects' brains, we calculated the Cronbach's α [11] of them. Specifically, for a set of signals X, which consists of K signals, S_i represents each signal column with n time points in Eq.(2).

$$X = [S_1, S_2, \dots \dots S_K], \quad S_i = [s_{i1}, s_{i2}, \dots \dots s_{in}]^T \tag{2}$$

The Cronbach's α is calculated as below, where $\sigma_{S_i}^2$ is the variance of each signal, and σ_X^2 is the variance of the signal set of X in Eq.(3).

$$\alpha = \frac{K}{K-1}\left(1 - \frac{\sum_{i=1}^{K} \sigma_{S_i}^2}{\sigma_X^2}\right) \tag{3}$$

In the following paragraphs, the Cronbach's α will be calculated as a measurement of the consistency of fMRI signals for each corresponding landmark, and it is also used as the measurement of the consistency of DFCs for each landmark-pair.

Specifically, in the first-stage, we extracted 358 cortical landmarks' fMRI signals for each subject in a group of n subjects. As each landmark possesses structural and functional correspondence across different subjects, for n fMRI signals of the same cortical landmark, we calculated their Cronbach's α to measure their consistency across subjects. With an experimentally determined threshold, we selected those landmarks with high fMRI signal consistency, and compared the averaged multi-subjects' signals of each selected landmark with the external stimuli curve. From this stage of analysis, we can determine the first-stage information processing centers.

In the second stage, we calculated the DFC time series with the sliding window length of 15 TRs (which is shorter than the length of any block type) via the methods in Section 2.4 for each landmark pair, in order to obtain their dynamic functional interaction patterns. Since the correspondences of cortical landmarks also apply to their corresponding connections, the group-wise consistent functional response analysis to corresponding connections is meaningful. Then for each landmark-pair connection *i*-*j*, we calculated the Cronbach's α of DFC time series from a group of n subjects to measure the functional interaction consistency. All of the connections are arranged into a 358×358 matrix. After we calculated the Cronbach's α for each connection, we obtained a matrix of α. Similarly, with an experimentally determined threshold, we selected the highly consistent dynamic interaction patterns between landmarks, and further compared them with the external stimulus curve. Strikingly, we found that these connections are either linked with the first-stage consistent information processing centers, or the ones starting from the first-stage information centers to other landmarks, which were thus determined as the second-stage consistent information processing centers.

3 Experimental Results

3.1 First-Stage Consistent Information Processing Centers

As described in Section 2.5, we calculated the Cronbach's α of fMRI signals for each corresponding landmark, and plotted them in Fig.3(a). Then, we used an empirical

threshold of α to select landmarks with high consistency of fMRI signals across subjects. In this way, we derived 35 consistently corresponding landmarks and further plotted their Cronbach's α values with blue stars in Fig.3(b). For each of the selected 35 landmarks, we averaged its fMRI signals from a group of 19 subjects and calculated the Pearson's correlation with external stimulus curve convolved with the hemodynamic response function (Fig.3(d)), which are represented by the red stars in Fig.3(b). From Fig.3(b), we can infer that most of the selected 35 landmarks with high Cronbach's α also exhibited high correlation (>0.5) with the stimulus curve. There are also 3 landmarks (illustrated by the black arrow in Fig.3(b)) that showed high anti-correlation (< -0.7) with the block-based stimulus. For visualization, we presented the locations of the 35 landmarks in Fig.3(g). Also, exemplar fMRI signal curves of the 35 landmarks are shown in Figs.3(e)-3(f), in which the green and yellow blocks correspond to the landmarks in green and yellow circles in Fig.3(g), respectively. These results demonstrate that the landmarks with high consistencies of fMRI signals across subjects either fit well with the stimuli curve as shown in Fig.3(e), or exhibit high anti-correlation with the stimuli curve as shown in Fig.3(f). Most of these selected landmarks either locate on the visual cortex or the frontal lobe, which are determined as the first-stage information processing centers. From a neuroscience perspective, it is reasonable that the 35 landmarks are selected as the first-stage information center since visual and frontal regions are likely to be the origins of bottom-up and top-down information sources in working memory processes [1-3].

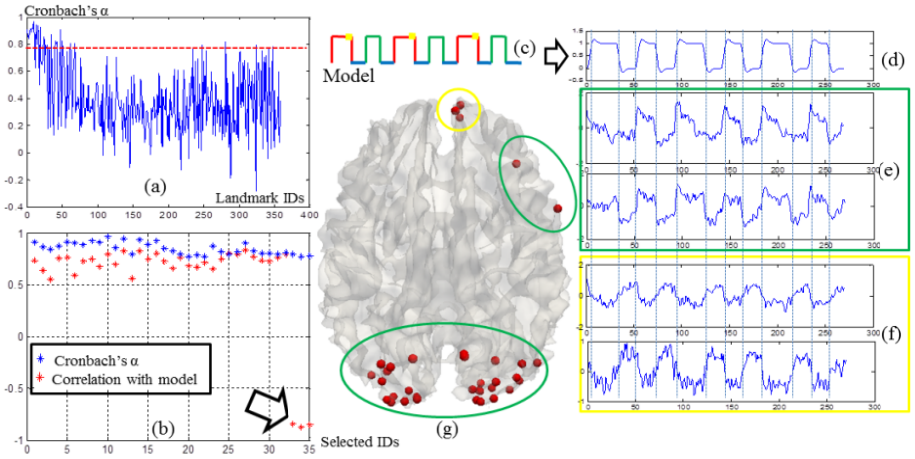


Fig. 3. (a) The curve of Cronbach's α for 358 cortical landmarks. (b) Selected 35 landmarks with high α values above the red dashed line in (a) and their Pearson's correlations with the stimulus curve. (c) Stimulus curve model. (d) Model convolved with HRF (hemodynamics response function). (e) Exemplar average fMRI signals of landmarks in green circles of (g). (f) Exemplar average fMRI signals of the landmarks in yellow circles of (g).

3.2 Second-Stage Consistent Functional Responses

In this stage, the consistency of DFC signals of each connection *i*-*j* was calculated via the method in Section 2.5 and the matrix of α is presented in Fig.4(a). We thresholded

the matrix of α and selected connections with high consistency of DFCs across subjects, as highlighted by the white elements in Fig.4(b). For neuroscience interpretation, they are further visualized in Fig.4(c), in which, the red spheres are the first-stage information centers obtained in Section 3.1 and the red lines are the connections with high consistency of DFCs. Figs.4(e)-4(g) show exemplar DFC signals of the selected connections and comparisons with the stimulus model. We found that these connections exhibit either high positive strength (Figs.4(e)-4(f)) or negative strength (Fig.4(g)) around the task change points, as illustrated by blue, green and red dashed lines. These results showed evidence that there are group-wise consistent interaction patterns among cortical landmarks, and these interactions exhibit high strength around task change points. From Fig.4(c), we can also infer that many of these interactions are among the first-stage information centers, and there are also some interactions spread to other cortical landmarks, which are determined as the second-stage information centers and will be discussed in details in the next section.

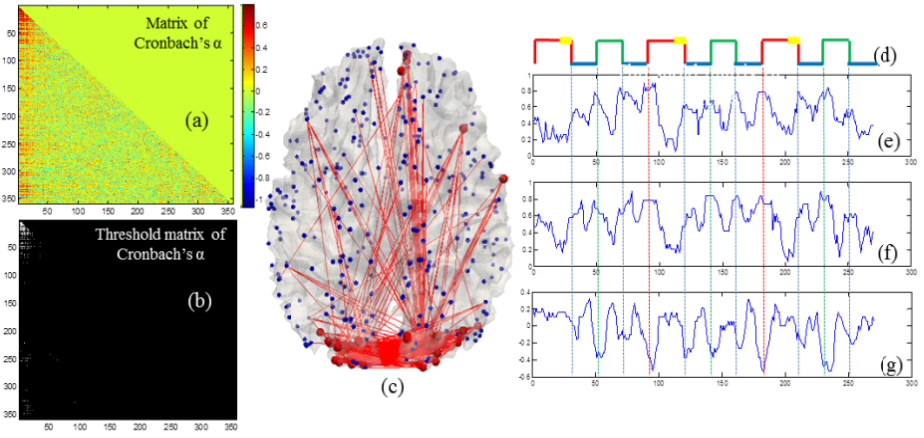


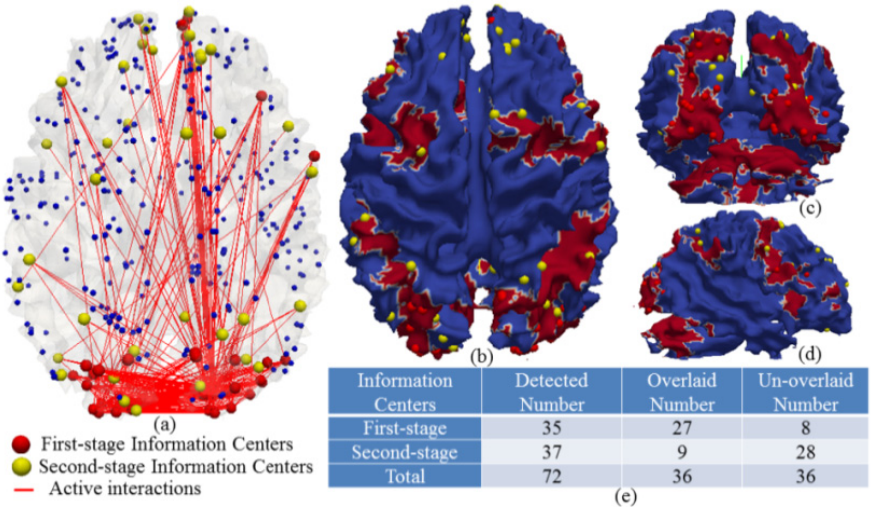
Fig. 4. (a) The matrix of Cronbach's α of DFCs among 358 landmarks. (b) Threshold matrix of (a). (c) Visualization of connections exhibiting high group-wise consistency with red lines. Blue spheres are 358 DICCCOL landmarks and larger red spheres are highlighted for the first-stage information centers. (d) Stimulus model. (e), (f), and (g): Exemplar average DFC signals of connections (red lines) in (c).

3.3 Hierarchical Functional Information Flows on Brain Networks

With the two-stage analyses discussed above, we detected the first-stage information centers with high consistency of fMRI BOLD responses (red spheres in Fig.5(a)) and second-stage connections with consistent functional interaction responses (red lines in Fig.5(a)). Furthermore, there are many other cortical landmarks (yellow spheres in Fig.5(a)) that are involved in the responding functional interactions, but not detected in the first-stage analysis. Here, we consider those yellow landmarks in Fig.5(a) as the second-stage information processing centers with more complex functional behaviors such as reverberation processes [1-3]. Essentially, they receive and process

information through the functional interactions with the first-stage information centers, and perform higher-level cognitive processes. Therefore, the visualizations of the two-stage information processing centers in Fig.5(a) reveal dynamic and hierarchical information flows during working memory task on large-scale landmarks.

In addition, for comparison, we performed group-wise activation detection using the FSL FEAT based on the GLM model and mixed-effect model [12] on fMRI volumes of the same dataset. We mapped the detected activations (p-value=0.05, z-value>3.5) to the cortical surface as red regions in Figs.5(b-d). We also overlaid our first-stage (red spheres) and second-stage (yellow spheres) information centers onto the same cortical surface. The comparison shows that the detected activations from FSL FEAT [12] coincide with most of our first-stage information centers. This means our first-stage information centers are mostly in agreement with traditional activation detection method. However, many second-stage information centers are outside of the activation areas by the traditional FSL FEAT. Quantitative results are provided in Fig.5(e). Here, 27 out of 35 first-stage information centers are overlaid with traditional activations, but only 9 out of 37 second-stage information centers are covered by traditional activations. These results demonstrate the advantages of our two-stage consistent response detection methods: it not only detects the responding brain regions that well follow the stimulus curve, but also other responding regions (*whose fMRI signals do not necessarily follow the external task stimulus curve*) that are in the down-streams of the dynamic and hierarchical cognitive processes.[1-3]



Information Centers	Detected Number	Overlaid Number	Un-overlaid Number
First-stage	35	27	8
Second-stage	37	9	28
Total	72	36	36

(e)

Fig. 5. (a) Illustration of dynamic and hierarchical information flows during working memory processes on cortical landmarks. (b) Comparison with traditional voxel-wise activation detection result by the FSL FEAT. Red areas of the cortical surface are activations and blue areas are not. (c)-(d) are two additional views of (b). (e) Numbers of information centers detected from two stages of analyses, and the number of overlaid landmarks with detected activations (red regions) in (b).

4 Conclusion

We presented a novel multi-stage consistent functional response detection framework to computationally model the dynamic and hierarchical cognitive processes. We used the publicly available DICCCOL brain localization and reference system to characterize the dynamic information flows on brain networks and determine the consistent functional responses. The working memory task-based fMRI data was used as an example, and experimental results demonstrated meaningful information flows during working memory task. In particular, qualitative and quantitative comparisons with traditional voxel-based activation detection via GLM demonstrated the superiority of computational modeling of dynamic and hierarchical cognitive processes, which is the major novelty and contribution of this work.

References

[1] Ward, L.M.: Synchronous neural oscillations and cognitive processes. Trends in Cognitive Sciences 7(12), 553–559 (2003)
[2] Lamme, V.A.F., Roelfsema, P.R.: The distinct modes of vision offered by feedforward and recurrent processing. Trends Neurosci. 23, 571–579 (2000)
[3] Varela, F., et al.: The brainweb: phase synchronization and large scale integration. Nat. Rev. Neurosci. 2, 229–239 (2001)
[4] Derrfuss, J., Mar, R.A.: Lost in localization: The need for a universal coordinate database. NeuroImage 48(1), 1–7 (2009)
[5] Friston, K.J., et al.: Statistical parametric maps in functional imaging: A general linear approach. Human Brain Mapping 2(4), 189–210 (1994)
[6] Zhu, D.: DICCCOL: Dense Individualized and Common Connectivity-based Cortical Landmarks. Cerebral Cortex (2012), http://dicccol.cs.uga.edu/
[7] Ohta, N., et al. (eds.): Dynamic cognitive processes. Springer (2005)
[8] Faraco, C.C., et al.: Complex span tasks and hippocampal recruitment during working memory. NeuroImage 55(2), 773–787 (2011)
[9] Liu, T., et al.: Brain tissue segmentation based on DTI data. NeuroImage 38(1), 114–123 (2007)
[10] Jenkinson, M., et al.: Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17(2), 825–841 (2002)
[11] Cronbach, L.J.: Coefficient alpha and the internal structure of tests. Psychometrika 16(3), 297–334 (1951)
[12] Beckmann, C.F., Jenkinson, M., Smith, S.M.: General multilevel linear modeling for group analysis in FMRI. Neuroimage 20(2), 1052–1063 (2003)