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Research report

An energy-efficient intrinsic functional organization of human working memory: A resting-state functional connectivity study

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HIGHLIGHTS

- The intrinsic functional organization of the human working memory remains unknown, we hypothesize that it is an energy-efficient system.
- We tested this hypothesis by analyzing associations between WM performance at different task difficulties and the FCD and FCS in 282 young adults.
- These findings suggest that the intrinsic working memory network is an energy-efficient and hierarchical system.

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ABSTRACT

Working memory (WM) is the active maintenance of currently relevant information that was just experienced or retrieved from long-term memory but no longer exists in the external environment; however, the intrinsic functional organization of the brain underlying human WM performance remains largely unknown. We hypothesize that the intrinsic functional organization of human WM is an energy-efficient system. We tested this hypothesis by analyzing associations between WM performance (reaction times of correct responses) at different task difficulties (2-back and 3-back tasks) and the resting-state functional connectivity density (FCD) and strength (FCS) in 282 healthy young adults. Voxel-based FCD analysis showed that the reaction times were negatively correlated with the FCD values of several brain regions known to be engaged in WM performance: the right inferior parietal lobule and inferior frontal gyrus for both the 2-back and the 3-back tasks and the right superior parietal lobule, supramarginal gyrus, left inferior parietal lobule and bilateral middle occipital gyrus for the 3-back task. Further analyses showed that the FCS values of these regions with several frontal, parietal and occipital regions were also negatively correlated with the reaction times; the 3-back task was associated with much more functional connections than the 2-back task. These findings suggest that the intrinsic working memory network is an energy-efficient and hierarchical system. A simple working memory task is controlled only by the core subsystem; however, a complex working memory task is associated with more nodes and connections of the system.

1. Introduction

Working memory (WM) is a limited capacity system that supports a variety of cognitive processes by temporarily maintaining and storing information [1,2]. The putative WM model comprises a central executive and three slave systems: the phonological loop, the visuospatial sketchpad and the episodic buffer [1–5]. WM performance could be measured by the n-back task, which requires the participants to supervise, update and manipulate the information being stored on-line [6].

The neural correlates of WM have been extensively investigated by task-based neuroimaging techniques. WM tasks consistently activate frontal and parietal areas, which are considered to be associated with WM performance [7–9]. The association between the fronto-parietal network and WM performance has also been revealed by volume [10] and white matter integrity [11,12] analyses. More importantly, WM task-based activation studies have

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Table 1
Demographic and behavioral characteristics of 282 healthy subjects.

	Mean ± SD	Range
Age (years)	22.7 ± 2.4	18–29
Education time (years)	15.6 ± 2.1	9–23
Handedness score	1.6 ± 0.8	1–3
Reaction time of correct responses (ms)		
2-back	720.1 ± 132.0	320–1037
3-back	753.5 ± 131.4	294–1114
Correct rate (%)		
2-back	89.3 ± 5.3	74.4–100.0
3-back	82.2 ± 6.4	61.1–95.6

shown that more difficult versions of the task activate more brain regions than simpler versions [7], suggesting that the brain activity within the WM network is in line with an energy-efficient pattern.

During task-free state, the intrinsic functional organization of the human brain is well-organized and can be assessed by resting-state functional connectivity, which characterizes the coherence of neural activity between brain regions within a specific functional network [13]. The activity [7] and topology [11,12] properties of the WM network or the whole brain network have been associated with WM performance. However, the association between connectivity properties and individual WM performance remains largely unknown. Based on the load effect of the WM tasks [14–17], we hypothesize that the intrinsic connectivity organization of the WM network shows an energy-efficient and hierarchical pattern. This predicts that a simple working memory task is controlled only by the core subsystem; however, a complex working memory task needs to recruit more nodes and connections of the system.

To test this hypothesis, we firstly investigated voxel-wise correlations between the functional connectivity density (FCD) [18] and WM reaction times (RTs) of correct responses of the 2-back and 3-back tasks in 282 healthy young subjects. We predict that the RT of the 3-back task may correlate with the FCD of more brain regions than the RT of the 2-back task. Then, we further tested correlations between the functional connectivity strengths (FCSs) of these regions and the RTs of the two tasks to identify the specific WM-related functional connections. We predict that the RT of the 3-back task may correlate with the strengths of more functional connections than the RT of the 2-back task.

2. Materials and methods

2.1. Subjects

A total of 306 right-handed healthy young adults were recruited for this study. Using a questionnaire (Table S1), participants were carefully screened to ensure that they had no history of psychiatric or neurological illness, psychiatric treatment, or drug or alcohol abuse and that they had no contraindications to MRI examination. All subjects were strongly right-handed according to the Chinese edition of the Edinburgh Handedness Inventory [19]. The study was approved by the Medical Research Ethics Committee of Tianjin Medical University, and all participants provided written informed consent. Twenty-four subjects were excluded from further analysis because of excessive head motion (13 subjects) or lack of evaluation scores (11 subjects). The remaining 282 healthy young adults (151 females and 131 males; mean age, 22.7 ± 2.4 years; range, 18–29 years) were ultimately included in the imaging analysis (Table 1).

2.2. N-back task experiment

The N-back task experiment was used to evaluate individual's WM performance [14,20]. A 2-back and a 3-back task were presented to individual subjects on a computer in a quiet room outside the MRI scanner, and the right side index finger and the middle finger of subjects were rested on two response buttons. During the task, subjects were instructed to press the right button with their middle finger if the letter that appeared on the screen was identical to the one observed either 2 (2-back) or 3 (3-back) letters earlier, and otherwise to press the left button with their index finger. Every N-back block (2-back or 3-back) lasted 60 s followed by a rest block of 20 s (Rest). The blocks were presented in a fixed order (2-back, Rest, 3-back, Rest, 2-back, Rest, 3-back, Rest, 2-back, Rest, 3-back, and Rest). Each letter stimulus was presented for 200 ms with an inter-stimulus interval of 1800 ms. Thus, there was a time window of 2000 ms for subjects to make a response. If a subject did not press the button within this time window, it was recorded "No Response", and the RT would not be recorded. Before the experiment, participants were verbally instructed and given 3 practice runs of the task. E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA, USA) was used to present the stimuli and collect the RT and correct rate (CR). The CR of each subject was calculated as the ratio between the number of hits and correct rejections and the total number of stimuli. The mean RT of correct responses was the sum of RT of correct responses (hits and correct rejections). The WM performance of each subject was assessed by the RT of correct responses, which can more accurately reflect WM performance than the mean RT of all responses by eliminating the effect of incorrect responses.

2.3. Imaging acquisition

MR images were acquired using a Signa HDx 3.0 T MR scanner (General Electric). Tight but comfortable foam padding was used to minimize head motion, and ear plugs were used to reduce scanner noise. Resting-state fMRI data were obtained using single-shot echoplanar imaging with the following parameters: repetition time (TR)/echo time (TE) = 2000/30 ms; field of view (FOV) = 240 × 240 mm; matrix = 64 × 64; flip angle (FA) = 90°; slice thickness = 4 mm; no gap; 40 interleaved transverse slices; and 180 vols. During the fMRI scans, all subjects were instructed to keep their eyes closed, to relax and move as little as possible, to think of nothing in particular, and to not fall asleep. To better coregister the fMRI data, sagittal 3D T1-weighted images were acquired using a brain volume (BRAVO) sequence (TR/TE = 8.1/3.1 ms; inversion time = 450 ms; FA = 13°; FOV = 256 × 256 mm; matrix = 256 × 256; slice thickness = 1 mm; no gap; 176 sagittal slices). Both the resting-state fMRI and T1-weighted data were visually inspected by a radiologist for apparent artifacts arising from subject motion and instrument malfunction. The head motion parameters of fMRI data were also tested immediately after the fMRI scan. If one subject's fMRI data did not satisfy the requirements, the fMRI scan was repeated once for the subject.

2.4. Data preprocessing

The resting-state fMRI data of 295 subjects (excluding 11 subjects without WM assessment) were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The first 10 vols for each subject were discarded to allow the signal to reach equilibrium and the participants to adapt to the scanning noise. The remaining 170 vols underwent slice-timing correction (sinc interpolation of all slices to the temporal midpoint of the first slice), accounting for differences in the acquisition time of each individual slice [21]. Rigid body realignment was used to correct for head motion, during which the 3 translational and 3 rotational motion parameters were computed [22]. The framewise displacement (FD), which indexes volume-to-volume changes in head position, was also calculated based on the head motion parameters [21,23]. The following steps were adopted to reduce head motion effects: (1) the fMRI data were excluded from further analysis if the maximum displacement in