Parkinsonism and Related Disorders 30 (2016) 46–51

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

# Impaired functional default mode network in patients with mild neurological Wilson's disease

Yongsheng Han [a, 1], Hewei Cheng [b, 1], Jon B. Toledo [c], Xun Wang [a], Bo Li [a], Yongzhu Han [a], Kai Wang [d, **], Yong Fan [e, *]

[a] Institute of Neurology, Anhui University of Chinese Medicine, Hefei, Anhui Province, China
[b] Department of Biomedical Engineering, School of Bioinformatics, Chongqing University of Posts and Telecommunications, Chongqing, 400065, China
[c] Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA
[d] Department of Neurology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui Province, China
[e] Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA

ARTICLE INFO

*Article history:*
Received 8 May 2016
Received in revised form
13 June 2016
Accepted 22 June 2016

*Keywords:*
Wilson's disease
Posterior cingulate cortex
Default mode network
Functional connectivity
Alerting efficiency

ABSTRACT

Wilson's disease (WD) is an autosomal recessive metabolic disorder characterized by cognitive, psychiatric and motor signs and symptoms that are associated with structural and pathological brain abnormalities, in addition to liver changes. However, functional brain connectivity pattern of WD patients remains largely unknown. In the present study, we investigated functional brain connectivity pattern of WD patients using resting state functional magnetic resonance imaging. Particularly, we studied default mode network (DMN) using posterior cingulate cortex (PCC) based seed functional connectivity analysis and graph theoretic functional brain network analysis tools, and investigated the relationship between the DMN's functional connectivity pattern of WD patients and their attention functions examined using the attention network test (ANT). Our results demonstrated that WD patients had altered DMN's functional connectivity and lower local and global network efficiency compared with normal controls (NCs). In addition, the functional connectivity between left inferior temporal cortex and right lateral parietal cortex was correlated with altering function, one of the attention functions, across WD and NC subjects. These findings indicated that the DMN's functional connectivity was altered in WD patients, which might be correlated with their attention dysfunction.



## 1. Introduction

Wilson's disease (WD) is an autosomal recessive metabolic disorder, characterized by cognitive, psychiatric and motor signs and symptoms and liver changes, due to excessive deposition of copper in the body, particularly the brain, the cornea, and the liver [1,2]. For WD patients with neuropsychiatric symptoms, the excessive copper in the brain causes neuronal injury, leading to motor, intellectual and behavioral dysfunction [3].

Structural and pathological brain abnormalities of WD patients have been documented in a number of neuroimaging studies [3–6]. Structural magnetic resonance imaging (sMRI) and diffusion tensor imaging (DTI) techniques have been used to investigate structural brain abnormalities in WD patients. Furthermore, metabolic brain abnormalities in WD patients have been investigated using positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) [7,8]. Most of these structural and pathological studies are case reports.

Similar to Parkinson's disease (PD) and Huntington's disease (HD), WD is also a basal ganglia disorder. In addition to motor symptoms, patients with these diseases show attention deficits [9–11]. It has been revealed that WD patients had longer overall mean reaction time (RT) and lower alerting efficiency in the attention network test (ANT) [12] than normal controls (NCs), indicating that WD patients have impaired attention functions, particularly alerting function [9].

The PD and HD patients with attention deficits have disrupted functional connectivity in DMN [13,14]. Furthermore, recent functional MRI (fMRI) studies have indicated that default mode network

* Corresponding author.
** Corresponding author.
*E-mail addresses:* wangkai1964@126.com (K. Wang), yong.fan@ieee.org, yong.fan@uphs.upenn.edu (Y. Fan).
[1] Equal contribution to this work.

http://dx.doi.org/10.1016/j.parkreldis.2016.06.018
1353-8020/

(DMN), particularly the posterior cingulate cortex (PCC), is associated with attention [15,16]. Therefore, we hypothesize that the WD patients with attention deficits also have the disrupted functional connectivity of DMN. In this study, we investigated WD patients' functional connectivity (FC) patterns of the PCC and DMN and their relationship with the attention functions based on resting state fMRI data.

## 2. Materials and methods

### 2.1. Subjects

Twenty four WD patients with brain disorders and 20 NCs matched in sex, age, education level, and intellectual level were included from a larger cohort [9]. The subjects included in the current study had small head motion when their fMRI scans were collected (the maximum displacement for brain voxels between different time points of fMRI scans was smaller than the voxel size). WD patients with brain disorders were recruited from the Institute of Neurology at Anhui University of Chinese Medicine in China. The WD diagnosis criteria were [17]: 1) presentation of extrapyramidal symptoms and signs, 2) corneal Kayser-Fleischer rings observed with a slit lamp, 3) serum ceruloplasmin<20 mg/dL or copper oxidase<0.21 mg/dL, and 4) a 24-h urinary copper concentration>100 μg. The exclusion criteria included: 1) patients with mental retardation (a score on the Wechsler Adult Intelligence Scale-Revised Chinese Version [WAIS-RC]-IQ<70 points), 2) patients with dysaudia and lalopathy, 3) patients with remarkable impairment of liver function (alanine aminotransferase>100 U or patients with liver cirrhosis), 4) patients with possible anxiety and depression symptoms (Hamilton Anxiety Scale (HAMA) [18] or Hamilton Depression Scale (HAMD) [19]>7 points), and 5) patients taking L-dopa or drugs that affect cognitive function. Particularly, the attention function could be affected by the increased dopamine concentration in the brain after taking L-dopa [20]. Every patient received regular copper chelation therapy, and no patient had visual acuity or field deficits. The United Wilson's Disease Rating Scale (UWDRS) was adopted to evaluate the entire spectrum of clinical symptoms for the WD patients [21]. The selected WD patients had mild symptom as reflected by their UWDRS scores (<30). They also had low prevalence of common WD symptoms and lower degree of resting tremor and postural tremor in the upper limbs, and did not show anxiety and depression symptoms. Matched NCs were recruited from a local volunteer group. All NCs were healthy, and none of them had a history of serious physical or mental illness.

The mental state of all the WD and NC subjects was evaluated using neuropsychological tests, including 1) WAIS-RC score for evaluating the intelligence [22], 2) HAMA and HAMD scores for evaluating anxiety and depressive states, respectively, 3) scores of verbal fluency tests (VFTs), including phonemic fluency and semantic fluency, for evaluating the frontal lobe function [23,24], and 4) scores of digit span tests (DTs), including forward and backward digits, for investigating short-term memory and attention span [25].

This study has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and received ethical approval from the Institutional Ethics Committee. Consent was obtained from all the subjects participated in this study.

### 2.2. Behavioral data of attention network test (ANT) acquisition

The ANT was used to assess each subject's attentional networks, including alerting, orienting, and executive control networks [12]. For each subject, efficiency of these attentional networks was measured. Particularly, efficiency of the alerting network was measured by changes in reaction time for a warning signal, efficiency of the orienting network was measured by changes in the reaction time to cues indicating where the target will occur, and efficiency of the executive network was measured by requiring the subject to indicate the direction of a central arrow surrounded by congruent, incongruent, or neutral flankers [9,12].

### 2.3. Imaging data acquisition

Imaging scans were collected using a 3T GE Signa scanner (GE Medical Systems) at the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui Province, China. A standard birdcage head coil was used, along with restraining foam pads to minimize head motion. Resting state fMRI scans were collected using a gradient echo-planar imaging (EPI) sequence (in-plane matrix = 64 × 64, 39 transverse slices with a slice thickness = 3 mm, repetition time [TR] = 2000 ms, echo time [TE] = 30 ms, field of view [FOV] = 240 × 240 $mm^2$, flip angle = 90°, voxel size = 3.75 × 3.75 × 3.8 $mm^3$). In addition, axial 3D T1-weighted images were obtained with a spoiled gradient recall sequence (TR = 7.01 ms, TE = 2.88 ms, flip angle = 8°, in-plane matrix = 256 × 256, slices = 166, FOV = 240 × 240 $mm^2$, voxel size = 0.94 × 0.94 × 1.2 $mm^3$).

### 2.4. Resting state fMRI data preprocessing

The fMRI data was pre-processed with following steps: 1) discarding the first 10 time points, 2) slice timing, 3) head motion correction, 4) intensity scaling of each fMRI scan after motion correction to yield a whole-brain mean value of 10000, 5) temporally band-pass filtering (0.01 Hz–0.08 Hz), 6) regression out of a set of nuisance signals including signal averaged over the white matter, signal averaged over the cerebrospinal fluid, global signal averaged over the whole brain, and six motion parameters, 7) nonlinear normalization into Montreal Neurological Institute (MNI) space with resolution 3 × 3 × 3 $mm^3$ using SPM8, 8) spatially smoothing with a 6 mm full width at half maximum Gaussian kernel. The nonlinear normalization of fMRI data was implemented using DARTEL of SPM8 with the deformation fields of their co-registered T1-weighted images. The head motion of fMRI scans was measured by the maximum displacement for brain voxels between different time points, and no statistically significant difference was found between WD (1.36 mm ± 0.73)) and NC (1.18 mm ± 0.77) groups ($p = 0.4266$).

### 2.5. PCC based functional connectivity analysis

The PCC is a central node of DMN, which has an important role in processing attention function [15]. Therefore, we chose the PCC as the seed region for the functional connectivity analysis. Particularly, the bilateral PCC as a whole region was selected as the seed region from AAL template [26]. For each subject, the mean time series of voxels in the PCC was used as the seed signal for computing whole-brain voxel-wise FC maps based on Pearson correlation. The resulting whole-brain voxel-wise FC maps were then transformed to z values using Fisher's z transform for subsequent statistical analysis.

The FC maps of PCC were compared between WD patients and NCs. Particularly, a two-tailed, one-sample *t*-test was firstly applied voxel-wisely to the whole-brain FC maps of all the subjects within each group, i.e., WD or NC, and brain regions with statistically significant functional connectivity were identified at a false-positive level of 0.05 according to Monte Carlo simulations with individual voxel threshold of $p < 0.05$. Then, the two-tailed, two-