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Original Article

Default mode network disturbances in restless legs syndrome/Willis–Ekbom disease

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ABSTRACT

Background: The unusual sensations of restless legs syndrome/Willis–Ekbom disease (RLS/WED) are induced by rest or a low arousal state with a circadian variation in the threshold for induction. It has been suggested that the emergence of RLS/WED symptoms relates to abnormal brain functions dealing with internally generated stimuli. The purpose of this study was to investigate the changes in the default mode network (DMN) in RLS/WED subjects.

Methods: Sixteen drug-naïve, idiopathic, RLS/WED subjects, and 16 age-matched and gender-matched healthy subjects were scanned in an asymptomatic resting state. A comparison of the DMN was conducted between the two groups. Resting state functional magnetic resonance imaging (MRI), Korean versions of the International RLS scale, and other sleep questionnaires were used.

Results: The results showed reductions in the DMN connectivity in the left posterior cingulate cortex, the right orbito-frontal gyrus, the left precuneus, and the right subcallosal gyrus of the RLS/WED subjects. The DMN connectivity was increased in sensory-motor-associated circuits, which included the right superior parietal lobule, the right supplementary motor area, and the left thalamus. In addition, the connectivity between the DMN and thalamus was negatively correlated with that in the orbito-frontal gyrus and the subcallosal gyrus in the subjects.

Conclusions: The results showed disturbances of the DMN in RLS/WED subjects that influence the thalamic relay sensory-motor-associated circuit. These findings may underscore the fact that RLS/WED subjects have disturbances in default mode network functions involving internal stimuli in the resting state. This may be related to compensatory changes to maintain resting.

1. Introduction

Restless legs syndrome/Willis–Ekbom disease (RLS/WED) is a neurological disorder characterized by an irresistible, compulsive urge to move the legs (limb akathisia). The sensation is triggered by rest, diminished arousal, or sleep [1]. Studies that have used a constant-routine paradigm with patients at rest over a 36-hour period or subjected patients to several hour-long periods of rest throughout the day have demonstrated that the propensity for symptoms is triggered by rest at any time of day, but the threshold for induction of symptoms as well as symptom severity appear to be under the control of circadian mechanisms [2,3]. Patients are most resistant to symptom induction by rest in the morning, and are at their lowest resistance in the evening. Equally relevant is that even simple external sensory input (eg, moving or rubbing of the legs) will completely eliminate the symptoms, as long as the stimulation is continued. Stop the stimulation, however, and the symptoms are likely to return almost immediately. The occurrence of RLS/WED sensory symptoms in the state of diminished external stimulation (ie, with rest) suggests functional abnormalities in the brain sensory/arousal systems. A functional neuroimaging study has demonstrated increased activation of the cerebellum and the thalamus during the presence of the RLS/WED sensory symptoms [4]. This study, while indicating brain areas associated with generation of RLS symptoms, failed to indicate mechanisms producing the rest-arousal dynamics inhibiting and exciting RLS symptoms.

During a resting period, brain connectivity changes provide one approach with which to assess the brain system dynamics of RLS/WED patients; this can be assessed by using an functional Magnetic Resonance Imaging (fMRI) during the period of greatest risk for RLS/

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WED symptoms. In comparison with healthy controls, RLS/WED patients have shown alterations during asymptomatic periods of resting state functional connectivity, which are associated with their symptoms [5]. Moreover, research examining the amplitude of low-frequency fluctuations (ALFF), before and after providing repetitive transcranial magnetic stimulation (rTMS) in the primary motor cortex, reported that there are intrinsic changes to the brain during the resting state in RLS/WED, and that modulating these changes improved RLS/WED symptoms [6].

The default mode network provides an alternate approach to examine brain connectivity in RLS/WED patients during rest. The default mode network (DMN) is a network of brain regions that has connectivity with the posterior cingulate cortex (PCC) during the resting state. Activity is mainly observed in the ventral medial prefrontal cortex (vMPC), the PCC, the inferior parietal lobule (IPL), the lateral temporal cortex (LTC), the dorsal medial prefrontal cortex (dMPFC), and the hippocampal formation (HF), which are active when the individual is not focused on the outside world and the brain is assumed to be in a state of wakeful rest [7,8]. The DMN, thus, represents connectivity of the cortical state of the brain under the full influence of rest or diminished external stimuli, which is also the state of the brain associated with triggering RLS/WED symptoms.

In the present study, it was hypothesized that RLS/WED patients, when evaluated during the asymptomatic period, would show: (1) differences in the functional connectivity of the DMN and (2) connectivity changes in other resting-state networks associated with the DMN. It was proposed that regional connectivity differences not ordinarily associated with the DMN represent compensatory mechanisms serving to suppress rest-engendered symptoms by directly regulating the resting state functional connectivity defined by the DMN. This study, therefore, assessed functional connectivity in RLS/WED patients during the morning asymptomatic period, in hopes of providing clues to the underlying mechanisms that play a role in keeping the symptoms in check, despite the provocative state of rest.

2. Methods

2.1. Study subjects

Resting-state fMRIs were obtained in the morning, to eliminate any influence from the patients' symptoms, from 16 patients with drug-naïve, idiopathic RLS/WED who visited a university hospital outpatient sleep disorder center, and also from 16 age-and-gender-matched healthy subjects who had no previous sleep problems and no other medical disorders. This study investigated the differences in the DMN between the two groups. The controls had answered "no" on the first two questions of the RLS Diagnostic Questionnaire: (1) Have you ever had unpleasant or uncomfortable feelings in your legs that occurred mainly while you were either sitting or lying down? (2) Have you ever felt the need or urge to move your legs that occurred mainly while you were sitting or lying down [9,10]? All patients were diagnosed through a clinical interview by a certified Korean neurologist, an expert in RLS/WED, during face-to-face interviews utilizing the validated Korean-language version [9] of the John Hopkins telephone diagnostic questionnaire [10]. Any mimic diseases, as required by the updated International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria [11], were excluded through face-to-face interviews and direct physical examinations. Patients with secondary RLS/WED due to pregnancy, iron-deficiency anemia, peripheral neuropathy, myelopathy, or chronic kidney disease were also excluded. However, subjects with only peripheral iron deficiency without definite cause were included. The severity of RLS/WED symptoms was evaluated from the validated Korean-language version [12] of the International RLS scale (K-IRLS) [13]. Other comorbid sleep disorders, such as circadian sleep disorders, parasomnia, and sleep apnea, were also excluded through validated Korean-language versions of sleep questionnaires, including: the Insomnia Severity Index (ISI-K) [14]; the Pittsburgh Sleep Quality Index (PSQI-K) [15]; the Epworth Sleepiness Scale (ESS-K) [16]; and polysomnography, if needed. The institutional ethics committee of the regional hospital approved the study. Informed consent was obtained from all participating subjects.

2.2. MRI protocol

Resting-state fMRI data were obtained in the morning between 09:00 and 12:00, prior to any caffeine consumption. MRI data were acquired using a 3 T MRI Signa Excite scanner (GE Healthcare, Milwaukee, WI, USA) with an eight-channel high-resolution brain coil. For each subject, an anatomic image series was obtained using a three-dimensional (3D) spoiled gradient-echo sequence (repetition time (TR) = 6 ms, echo time (TE) = 2.2 ms, flip angle = 20°, field of view = 240 mm, 256 × 256, 152 axial slices, slice thickness = 2 mm thick). The functional images were collected using a gradient echo planar imaging (EPI) sequence (TR = 2000 ms, TE = 17.6 ms, flip angle = 90°, field of view = 240 mm, matrix = 64 × 64, slice thickness = 4 mm, no gap, 244 scans of 30 contiguous axial slices) during a period of approximately eight minutes. During the scan, subjects were asked to close their eyes without sleeping. The methods required excluding patients who fell asleep during the scan, however, this did not occur. In addition, none of the RLS/WED patients reported RLS/WED symptoms immediately prior to, during, or immediately after the MRI scan.

2.3. Analysis of resting-state fMRI

Resting-state fMRI data were processed using Analysis of Functional Neuroimage (AFNI) software [17]. The first four time points in all of the time series dataset were discarded. The analysis comprised slice time correction for interleaved acquisitions, despiking, 3D motion correction (head movement was <2.5 mm), temporal normalizing, linear and quadratic detrending, spatial normalization using the Montreal Neurological Institute (MNI) 152 template provided in the AFNI package, spatial smoothing (full width at half maximum 6 mm), and temporal filtering (0.009–0.1 Hz).

For extracting the DMN from the resting-state fMRI, the analysis protocol used by Hahn was followed, which is based on the several steps of seed-based resting-state connectivity analysis to reduce seed-selection bias [18]. Following this method, the first seed region was defined within the posterior cingulate cortex (cubic volume of 3 × 3 × 3 voxels = 216 mm^3 centered at x, y, z = 0, –52, 30 mm); a second region was defined within the medial prefrontal cortex (cubic volume of 3 × 3 × 3 voxels = 216 mm^3 centered at x, y, z = 0, 50, 22 mm). The whole brain voxel-wise correlations associated with the mean time series for each of the two seed regions were computed using 3dDeconvolve (AFNI). At this step, predictor regression analyses were used to control for effects of nine different artifacts (ie, white matter, cerebrospinal fluid, global signal, and six motion parameters). The correlation maps were converted to *Z*-value by Fisher's r-to-z transformation. Two binary maps of the DMN were obtained by applying a one-sample *t*-test across subjects (family-wise error (FWE) corrected *p*-value <0.05). Then the final seed regions for each group (RLS/WED patients, controls) were calculated as the intersection of the two binary maps, covering a volume of 47.6 cm^3 (=5952 voxels) for the patients group, and 40.4 cm^3 (=5056 voxels) for controls. Hence, the obtained seed was not restricted to a particular region, but comprised a conjunction of several network nodes. The whole brain voxel-wise correlation for the mean time series of the final seed region was computed and