

# Effective Connectivity within the Papez Circuit in the Multiple Sclerosis Patients: A Comparative Study Using Resting-State fMRI

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## ABSTRACT

**Background:** Multiple sclerosis (MS) disease causes structural and functional damage to brain. Structural imaging of the MS-induced damage cannot adequately describe the functional impairment of the brain in MS patients. Therefore, it seems that advanced functional imaging analysis such as functional magnetic resonance imaging (fMRI) data is needed for better management of this disease.

**Objective:** The aim of present study was to evaluate the effective connectivity within the Papez circuit in MS patients using resting-state fMRI.

**Material and Methods:** In this cross-sectional analytical study, 22 healthy individuals and 24 patients with MS underwent resting-state fMRI. After pre-processing of the obtained data, the time series of Cingulate gyrus (CG), Para hippocampus gyrus (PHG), anterior thalamic nuclei (ATN), Mammillary body (MB), and Hippocampus (HPC) were extracted as the main Papez circuit components. The obtained time series were statistically analyzed as an input of the dynamic causal model in order to evaluate the effective connectivity in the Papez circuit.

**Results:** The power of effective connectivity between each pair of tested nodes in Papez circuit was significantly lower in MS patients than healthy subjects. Also, the effective connectivity level of MS patients in direction of HPC→ATN was higher in men than women. In addition, effective self-connection in CG→CG and MB→MB regions in healthy subjects were higher in women than them in men.

**Conclusion:** The present study reveals significant difference in effective connectivity of the Papez nodes in MS patients than control group, which can be exploited to diagnosis and predict or evaluate the treatment response of these patients.

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## Keywords

Functional Neuroimaging; Magnetic Resonance Imaging; Multiple Sclerosis; Brain; Effective Connectivity

## Introduction

Multiple sclerosis (MS) disease is caused due to demyelination in the nervous system and can delay or stop the transmission of the action potential along the nerves, leading to structural and functional damage to the brain. This autoimmune and inflammatory disease also impairs effective connectivity, resulting in many

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signs and symptoms of physical, psychological, emotional, and cognitive disabilities [1]. More than 2.5 million people worldwide are affected by this disease [2]. Structural imaging of the Magnetic Resonance Imaging (MRI) is the most common method to diagnose the MS; however, this method is not able to diagnose the disease in early stages [1, 2]. The structural imaging also cannot adequately describe the functional impairment in brain of these patients; in addition, small lesions are not detected by MRI [1, 3]. Another problem is that the pathological symptoms of the MS patient are similar to other neurological diseases, thus MS illness can be misdiagnosed [1, 3]. The common clinical symptoms of MS are: numbness or weakness in one or more limbs, electric-shock sensations that occur with certain neck movements, vision problems, slurred speech, fatigue, dizziness, tingling or pain in parts of the body, problems with sexual, bowel, and bladder function, muscle stiffness or spasms, and paralysis typically in the legs. Therefore, various methods such as positron emission tomography (PET) scan, electroencephalography (EEG), and Magnetoencephalography (MEG) have been exploited to identify brain activity and the neurological diseases. Functional MRI (fMRI) as a non-invasive method has been also used more, which is mainly based on a phenomenon known as Blood Oxygenation Level Dependent (BOLD) effect and uses the differential magnetic properties of deoxygenated and oxygenated hemoglobin as an endogenous source of contrast in blood [1-3]. The fMRI technique, given the proper spatial and temporal resolution, is one of the new techniques for displaying brain activity. The fMRI imaging is done in both the task base and resting-state. In resting-state fMRI (rs-fMRI) imaging, because there is no need to perform any specific task or activity, imaging can be taken simultaneously with other modulators in clinical trials. However, in both resting and dynamic states of brain, the innate activity of brain is not fully understood; it has

been shown that disorders affecting the recognition and diagnosis, such as MS illness, will also interfere with the resting state of brain [3].

Brain activation map as well as the types of connectivity within a nervous system, including functional connectivity and effective connectivity in brain can be extracted using the rs-fMRI [4, 5]. Functional and effective connectivity allows further investigations of neural networks. Functional connectivity monitors brain regions that do not have a well-known anatomical relationship, in which the data analysis gives information on how the brain area works, forming a network [4]. While, effective connectivity examines the effect of a region on a given area during a certain neuronal process. Therefore, analysis of effective connectivity is the best method for investigating the dynamic interactions between brain regions when individuals are busy in certain cognitive processes or even in rest [5]. Former studies on MS patients have shown an increase or a decrease in functional connectivity in various brain regions [6] i.e. lower functional connectivity between the right and left primary motor cortices than healthy subjects has been reported [7]. Other studies have also reported changes in the functional pattern of brain in patients with MS [8]. An effective connectivity study on MS patients indicates that patients with MS who have defective processing speed comprise both numerous and powerful connectivity than either healthy subjects or other MS patients without any defect in processing speed [5].

In studies conducted on MS patients with focusing on limbic system, the relatively high incidence of lesions that may lead to memory loss, olfactory dysfunction, reward defects, impaired excitement, and cognitive function have been reported [9]; these findings reveal the interference of MS disease with limbic system lesions. Papez circuit is a part of the limbic system, and previously it was thought that it is only related to emotional and cognitive behaviors. However, scientists have recently

shown that the Papez circuit is also responsible for control of memory, reward, cognition, and olfaction [10]. Although it is clear that the Papez circuit in brain is of particular importance, especially in MS patients, there are not enough fMRI data, clarifying the effective connectivity of Papez circuit segments in these patients. This study was conducted to analyze the effective connectivity of the Papez circuit in patients with MS compared to healthy individuals using the rs-fMRI method.

## Material and Methods

### Subjects

In this cross-sectional analytical study, 22 healthy subjects and 24 MS patients, 30-35 aged, were randomly selected. Healthy individuals were included 17 women and 5 men, and the group of MS patients was included 16 women and 8 men. All participants were admitted in the Sina MS Research Center, Sina Hospital-Tehran, Iran over the past three years. The research was conducted after approving by the Medical Ethics Committee of Kermanshah University of Medical Sciences (IR.KUMS.REC.1397.414) in accordance to the Helsinki Declaration. All of subjects in our study were Persian and Right-handed. None of the studied subjects had a history of alcohol abuse, addiction, neurological, metabolic and psychological problems, based on their medical history and examinations. MS diagnosis was performed with McDonald's criteria [11], and none of the patients had a recurrence evaluation and or imaging during the previous 6 weeks before rs-fMRI. Written consent was given to participants after complete and transparent statements, and all of the participants were able to understand and follow the description. Moreover, a general description of the imaging process was given to the participants before rs-fMRI. After placing the subjects inside the MRI scanner, they were asked to close their eyes so that they could not even activate the visual area in their brains. They

were also requested to be completely comfortable and quiet (no motor areas and no physical activity). In addition, individuals were asked not to deliberately think about a specific issue so that areas of thinking and memory in their brain would not be active. The duration of imaging for each volunteer was about 15 min and all of participants were able to understand and follow the imaging steps.

### fMRI data acquisition

The data of functional and structural imaging were collected using a 3 Tesla Siemens scanner (3T Platform, SIEMENS, and Germany). The rs-fMRI data were obtained using the gradient-echo echo-planar imaging (GE-EPI) technique via the following parameters: TR=2.2 Sec, TE=30 ms, flip angle= 90°, matrix size=64×64, voxel size=3 ×3×3 mm<sup>3</sup>, 40 slices, slice thickness=3 mm, slice gap=0, slice sequence: interleaved. The structural images were acquired using a high resolution three dimensional T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence with the following scan parameters: TR=2.53 Sec, TE=3.44 ms, flip angle =7°, matrix size=256×256, voxel size=1×1×1 mm<sup>3</sup>, 176 slices, slice thickness=1 mm. Structural T1-weighted high-resolution images were used for registering images on each person's brain.

### Pre-processing

In present study, the Data Processing Assistant for Resting-State fMRI (DPARSF) toolkit [12] was used to perform all of the preprocessing steps, including converting DICOM to NIFTI, slice timing, head motion correction, normalization, removing the linear trend, filtering. Since the most of scanners produce images in DICOM format, it must be converted to other formats such as NIFTI before analyzing the data. The NIFTI format with the nii extension has four dimensions, three of which relate to the structural dimensions of the image and the fourth dimension is the time, or

data of volumes of the brain that have been acquired over the time of imaging. The initial ten volumes of functional images were discarded for signal equilibrium and allow the participants to adapt to the initial scanning noise and balance the magnetic field. Slice timing correction (STC) was also done due to the slice-dependent delays, in which achieved by shifting the time series of each slice to temporally align all slices to a reference time-point. STC becomes more important when the repetition time (TR) is long and there is a possibility of a significant change in hemodynamic response between slices. Small movement of patient's head during imaging can be a major source of error; when the motion occurs, signal of a particular voxel will be infected by the neighbors' voxel signal. Therefore, the accurate estimate of the amount of head motion for correction is very important. In the present study, the data from individuals entered the study in which the translational and or rotational motions of the head were less than 1.5 mm in all directions.

The fMRI data typically has a limited spatial resolution and provides low anatomical information; thus, the obtained functional data were registered to the anatomical MRI images in normalization stage. The process of registering images of anatomical and functional images is called co-registration [13], which is usually done by Rigid-body transformation in three dimensions using six parameters or Affine transformation with 12 parameters, including three translation, three rotation, three scaling, and three skew parameters; the Affine transformation was used in present study. Because the size, shape, orientation, and anatomy of the brain vary from one person to another person, the images were considered spatially in a standardized format of the Montreal Neurological Institute (MNI) in order to make the comparison possible. A band-pass filter (0.01-0.08 Hz) was also used in order to eliminate the effects of low-frequency drift and physiological noises due to gradual changes in the

brain.

The quality control score following completing the pre-processing steps was calculated using the DPARSF toolkit for all subjects; that was 5, meaning a very good score. The purpose of pre-processing fMRI data is to obtain the most appropriate time series of each voxel in all subjects that are needed in the other steps of effective connectivity analysis.

### Effective connectivity evaluation

To describe effective connectivity, a model for interconnecting neuronal units is needed that includes two features: a model of activity of neuronal populations that is acceptable from a neurobiological point of view; and a feed-forward model that is biophysically acceptable and the changes of the nervous activity corresponds to the measured signal. The dynamic causal modeling (DCM) method has the both features. DCM is used to determine the effective connectivities among brain regions by analyzing fMRI data. and also is a type of biophysical and neurobiological modeling, using basic information for model selection [14]. This model simulates the connections of these regions using nonlinear mechanisms based on the blood-dependent changes in nodal points of regions of interest (ROIs). Therefore, the effective connectivity within the Papez circuit in MS patients and healthy subjects as control group was investigated using the DCM method in this study. To calculate the effective connectivity values of the brain regions within the Papez circuit, the SPM12 toolbox (with Update Revision Number of 7487) was used. The DCM analysis steps with the SPM12 toolbox include the following steps:

1. *Selecting ROIs*: To calculate the DCM model after the pre-processing the data, the brain regions (i.e. ROIs) must be identified to determine the relationships among these regions. However, given the heavy computational constraints in DCM analysis, many ROIs cannot be selected. The ROIs in the present study are those areas corresponding to the



Papez circuit, the MNI coordinates of these regions and their spatial position in brain are shown in Table 1 and Figure 1, respectively.

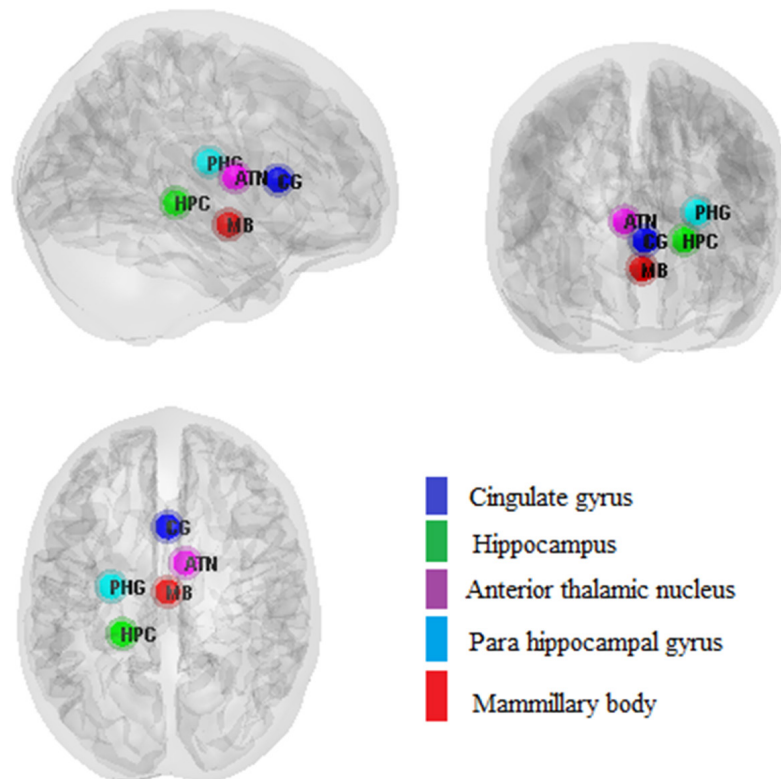
2. *Papez circuit time series extraction:* The time series represents blood hemodynamic changes (BOLD changes) over the time of imaging. According to Biswal et al. study [15], which showed that the frequency range containing the useful information of the BOLD

signal is 0.08 to 0.01 Hz; time series of each area (BOLD variations as a function of time) were extracted using the Fourier transform in this frequency range; and then these time series were used as inputs for model estimation in the present study.

3. *Model determination:* A DCM was initially created with all the features of internal connectivity as a complete model for each per-

**Table 1:** The Montreal Neurological Institute (MNI) coordinates for Papez circuit.

Brain regions	Abbreviation	Location(mm)		
Cingulate gyrus	CG	0	16	7
Hippocampus	HPC	-21	-31	-8
Mammillary body	MB	0	-7	-14
Para hippocampal gyrus	PHG	-26	-16	-10
Anterior thalamic nucleus	ATN	8	-4	10



**Figure 1:** Five regions of interest (ROI) within the Papez circuit that were used to analyze the dynamic causal modeling (DCM)

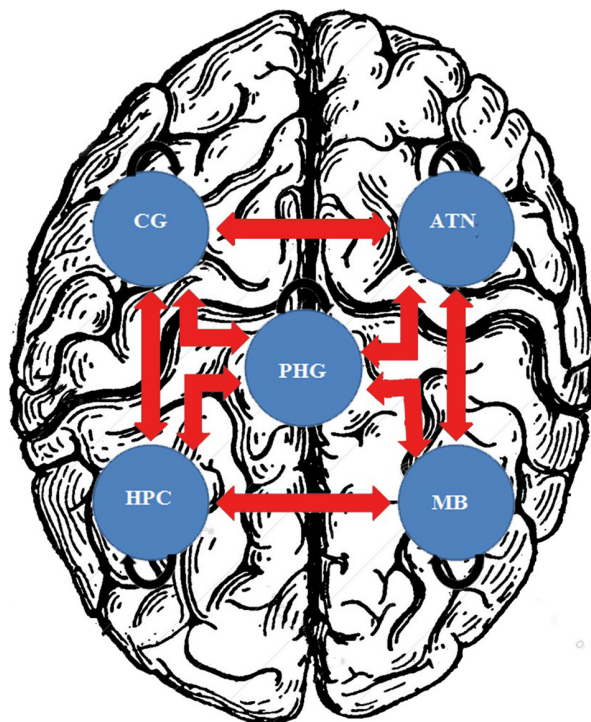
son. The DCM spectrum framework was used to invert each person's model [16]. Then, network discovery method for optimizing DCMs was also used for both of MS and control groups [17]. This widely used method in neuroscience research tests all existing models in the complete model and chooses the optimum model with the highest posterior probability [18].

4. *Graph determination of the effective connectivity by DCM:* The model of neuronal state equations [19] was used to determine the effective connectivity graph of each individual. An effective brain network was estimated for all individuals in both healthy and MS groups using the DCM model. False discovery rate (FDR) with  $p < 0.05$  was used to analyze the group. The power of effective connectivity of Papez-related brain network in the DCM model of healthy subjects and MS patients was compared using Bayesian parameter averaging (BPA) method [20].

The main aims of the present study were: the evaluation and comparison of the effective connectivity within the Papez circuit in healthy and MS patients, evaluation and comparison of the effective connectivity within the Papez circuit in women and men in MS patients, and evaluation and comparison of the effective connectivity within the Papez circuit in women and men in healthy individuals.

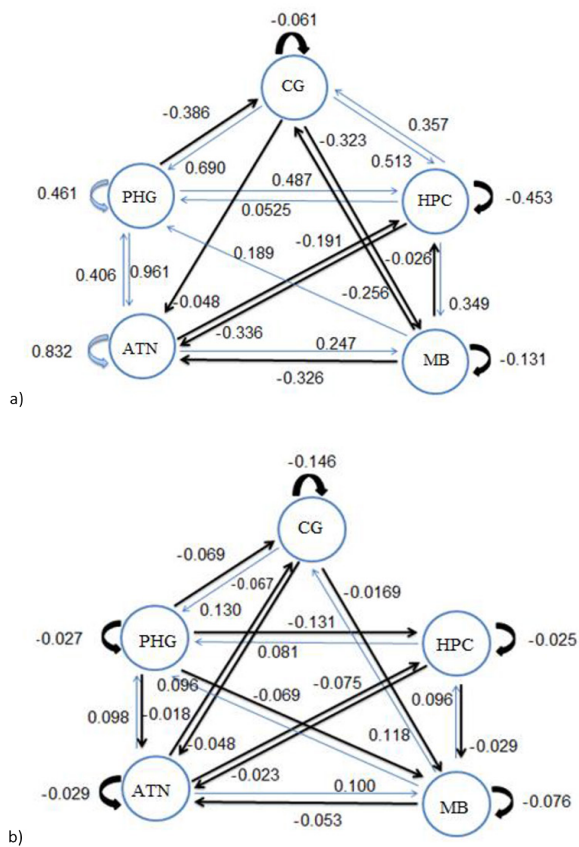
## Results

The time series of the corresponding areas of the Papez circuit were extracted as inputs of the DCM model after preprocessing the data of two healthy groups and MS patients and the effective connectivity values of these brain regions (Figure 2) were calculated. The optimum models of effective connectivity for healthy subjects and MS patients are obtained and shown graphically using the RFX analysis method in Figures 3a and b that demonstrate the relationship of self-connection regions, meaning the effect of neurons of each region on themselves and the connections between



**Figure 2:** The dynamic causal modeling (DCM) model for effective connectivity estimation in the Papez circuit

the two regions; meaning the effect of neurons in one region on another one. After obtaining the effective connectivity values of the Papez circuit using the DCM method, statistical analyses were carried out. For this purpose, the statistical distribution of obtained data of each group was investigated using Kolmogorov-Smirnov test. Then, statistical T-test (Student's T-Test) or non-parametric U-Mann-Whitney tests were used for comparing the mean of effective connectivity values between pair different groups. Based on the results, effective connectivity level in CG→CG, CG→PRHIP, MB→MB, MB→PRHIP, ATN→MB, ATN→HPC, PHG→ATN, ATN→ATN, CG→MB, CG→ATN, CG→HPC, MB→ATN, HPC→HPC, HPC→ATN, HPC→PHG, PHG→PHG, and PHG→HPC regions were significantly different in healthy individuals than MS patients ( $P < 0.05$ ). The power of



**Figure 3:** Showing the optimal extracted final model of effective connectivity; Normal subjects (a) and Multiple sclerosis (MS) patients (b). The blue arrows indicate positive, while the blacks demonstrate negative effective connectivity. Numbers represent the mean effective connectivity power extracted from the Bayesian method. Positive values illustrate an increase, while the negative values indicate decreasing in the effective connectivity level

effective connectivity between each pair of these nodes in Papez circuit was significantly lower in MS patients than healthy subjects. Also, results showed that only in HPC→ATN region, there was a significant difference in the effective connectivity between the two groups of men and women in MS patients, in which the effective connectivity level was higher in men than in women. There was also difference

in the mean of effective connectivity power in MB→MB and CG→CG regions of healthy individuals, brain, which can be called as effective self-connection, between men and women ( $P < 0.05$ ), in which the mean of effective connectivity level in men was lower than that in women.

### Discussion

In the present study, different effective connectivities in the Papez circuit nodes were investigated using fMRI in MS patients and normal subjects. The significant differences in gender-related characteristics were also seen in effective connectivities within the Papez circuit. MS is associated with a high incidence and mortality rate worldwide and great deal of effort has been presumed to overcome this neuroinflammatory disease; however, we could only relief the sign and the symptoms of the illness up to now and the final treatment approaches are unclear [21]. The cellular and molecular cascade, involved in MS, is fundamental for distinguishing its initiation, progression, outbreak, and cure. The processes, including mitochondrial dysfunction, systemic inflammation, oxidative stress, a range of autoimmune phenomena, and hypothalamic-pituitary axis dysfunction induce catastrophic outcomes in some parts of central nervous system (CNS) [22]. It seems to be necessary to evaluate the association of the nervous damaged area with the clinical symptoms in MS patients as future studies in MS management. Drawing this future insight would be done with a series of experimental studies (on animal models), then with conducting clinical trials. Nevertheless, the histological lesions in animals and their consequence symptoms would not be completely as the same as those that occur in human [23, 24].

Neuroimaging based techniques as another approach for MS management can shorten the selection or suggest an effective strategy for the treatment of each patient with outbreak of certain symptoms [25]. It seems that there is

no need for histopathological evaluation for determining the regions involved in MS or other neurological disorders using the optimum method of this approach. Thus, the all that therapist must do is to monitor the nervous system as a whole and also to consider the symptom of disease. This simplified and precise method of treatment arises from the fact that each neuroanatomical portion with its own function would be observable by neuroimaging based techniques. Thus, any occurrence of tissue stricken guides the therapist for the remedy, and the symptoms proof that fMRI is the most astute method among neuroimaging techniques; fMRI makes us capable of evaluating the both of functional and effective (quantitative) connectivity between centers or nodes of nervous system [26]. It means that fMRI specifies the location of lesion and the impaired connection with the other nodes of the nervous system, and finally characterizes the exact amount of these misconnections. This method is such accurate that can compare the gene expression level with a special node activity of neurological disorders like schizophrenia [27]. Functional disconnection between large-scale resting-state neural networks is a characteristic feature of relapsing-remitting MS (RRMS) in the advanced stage of the disease. Moreover, the degree of segregation correlates with the severity of disability in multiple dimensions and also with the extent of T2-lesion load [28]. The clinical significance of these abnormalities demonstrates that functional and effective connectivity between networks is significantly stronger in patients with preserved cognitive function and correlates with lower lesion load and other structural abnormalities [29].

However, the limitation of fMRI is related to new symptoms of neurological disorders that would bewilder the therapists to adjust the new symptoms with the common area influenced by MS [30]. Nowadays, the McDonald criteria are performed by incorporating clinical evaluation with magnetic resonance

imaging (MRI) scans in distinguishing MS [31]. However, above mentioned the common symptoms are mainly related to destruction in sensory or motor areas of CNS; other symptoms in MS patients such as depression, epilepsy, chronic fatigue, forgetfulness or mood swings that may be related to injury to Papez circuit would confuse the medication method [32]. Papez circuit, a region of limbic system in brain discovered by James Papez in 1937 [33], has many nodes controlling spatial and episodic memory, emotional behavior, and language learning [10]. Recently, the correlation between MS with disorders of Papez-circuit region has been reported [34]. In present study, the Papez circuit nodes in MS patients were considered and the effective connectivities of these nodes were extracted. The most important finding of the present study is that effective connectivity among the regions within Papez circuit with direction CG→CG, CG→PRHIP, MB→MB, MB→PRHIP, ATN→MB, ATN→HPC, PHG→ATN, ATN→ATN, CG→MB, CG→ATN, CG→HPC, MB→ATN, HPC→HPC, HPC→ATN, HPC→PHG, PHG→PHG, PHG→HPC, significantly differs between normal subjects and MS patients, which have lower levels in MS group. Since both groups were examined using resting-state fMRI, confounding variables such as sensation, cognition, and movement were omitted; and thus, we can say that Papez circuit is an area that could be hurt in MS patients with any signs and symptoms, although the indication of Papez circuit-related symptoms may be observed in later stage of this illness. To the extent of our knowledge, these data are unique with regarding the evaluation and calculation of functional and effective connectivities of different nodes in Papez circuit; another unique finding of the present study is that only in HPC→ATN region, there was a significant difference in the effective connectivity between the two groups of men and women in MS patients. Thus, we can say there are the relatively same pattern of



effective connectivity in the Papez circuit regardless of sex and the effective connectivity assessment could be considered as proper diagnostic tool in patients with MS. Also, effective self-connection in the CG → CG and MB → MB regions in healthy subjects are higher in women than those in men; one of the reasons for this difference between males and females may be the corpus callosum in the brain, connecting the left and right hemispheres, thus is larger in females than males [35].

A combination of fMRI and diffusion tensor imaging (DTI) studies on 18 MS patients and 16 healthy individuals demonstrated the relationship of structural damage to the Papez circuit called the fornix, which correlates regions of this circuit with memory function [36]. The observed increase in the severity of MB self-loop in MS patients as well as the increased association of this area with other regions, is probably due to the decreased volume of this area in these patients according to recent studies [37]. In this study, a decrease in the severity of CG self-looping was observed in patients with MS based on several fMRI studies performed on MS patients, and it can be concluded that this decrease may be due to increased CG activity in patients with MS [38]. Because of widely demyelination of the hippocampus in MS [39], effective connectivity of HIP→CG as well as CG→HIP was found in healthy individuals with high severity than of patients with MS. Also, the relationship between hippocampus and other areas changed in the patients.

## Conclusion

The present study reveals significant difference in effective connectivity of the Papez nodes in MS patients than control group. However, future advanced functional imaging analysis and measurements on other regions in brain as well as present study that was done on the Papez circuit are strongly needed in order to better understand the mechanism and damage underlying to MS, so that the significant

difference in MS patients than normal individuals can be exploited to better diagnosis and predict or evaluate the response to treatment of this illness.

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## Authors' Contribution

M. Siyah Mansoori conceived the idea. The paper was written and revised by K. Khoshgard, M. Siyah Mansoori, and A. Chehreh. A. Chehreh, M. Siyah Mansoori and A. Ebrahiminia gather the images and the related literature. The method implementation was carried out by A. Chehreh, M. Siyah Mansoori and K. Khoshgard. Results and data Analysis was carried out by K. Khoshgard, I. Rashidi, and A. Chehreh. The research work was proofread and supervised by K. Khoshgard and M. Siyah Mansoori. All the authors read, modified, and approved the final version of the manuscript.

## Ethical Approval

The Ethics Committee of Kermanshah University of Medical Sciences approved the protocol of the study (Ethic cod: IR.KUMS.REC.1397.41).

## Informed consent

Written informed consent was given to all of the participants after complete and transparent statements. Participating in the study was fully voluntary; also, there was no cost for participating in this study.

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## Conflict of Interest

None

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