Does Lexical Retrieval Deteriorate in Patients with Mild Cognitive Impairment? Analysis of Brain Functional Network Will Tell

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Abstract

Alterations in speech and language are typical signs of mild cognitive impairment (MCI), considered to be the prodromal stage of Alzheimer's disease (AD). Yet, very few studies have pointed out at what stage their speech production is disrupted. To bridge this knowledge gap, the present study focused on lexical retrieval, a specific process during speech production, and investigated how it is affected in cognitively impairment patients with the state-of-the-art analysis of brain functional network. 17 patients with MCI and 20 age-matched controls were invited to complete a primed picture naming task, of which the prime was either semantically related or unrelated to the target. Using electroencephalography (EEG) signals collected during task performance, even-related potentials (ERPs) were analyzed, together with the construction of the brain functional network. Results showed that whereas MCI patients did not exhibit significant differences in reaction time and ERP responses, their brain functional network did alter associated with a significant main effect in accuracy. The observation of increased cluster coefficients and characteristic path length indicated deteriorations in global information processing, which provided evidence that deficits in lexical retrieval might have occurred even at the preclinical stage of AD.

Index Terms: mild cognitive impairment, speech and language impairment, event-related potentials, brain functional network

1. Introduction

As the most common type of dementia, Alzheimer's disease (AD) manifests itself in functional performances in multiple cognitive domains. Although memory impairment due to damage of the medial temporal lobe is the characteristic symptom of AD, disorders in speech and language are also prevalent. Previous studies have shown that speech and language deficits in AD patients are caused by a decline in lexical semantic abilities, whereas functions in phonological and syntactic processing are spared at the early stage of disease [1]. Compared to the evidence of how speech and language functions become affected in patients with AD, very few studies focused on its prodromal stage, often known as mild cognitive impairment (MCI), due to the fact that impairment at this stage is not sufficient to impact day-to-day activities. This knowledge gap motivates the present study with an open question: does lexical retrieval, the most vulnerable stage during speech production, begin to deteriorate even at the stage of MCI?

A number of theories have posited that speech production involves various stages, each of which is in sequential order. The computation model WEAVER++ (an abbreviation for Word-form Encoding by Activation and VERification) [2] together with confirmations using analytic techniques with high temporal resolution (e.g., electroencephalography, EEG) [3] have elucidated how word meanings (lexical concepts and lemmas) are translated into speech sounds. For the process of picture naming, for example, lexical retrieval occurs soon after the presentation of picture stimuli (usually within about 175 ms), with the appropriate sound being encoded between 250 and 300 ms post stimulus. After that, word in its phonological form is generated (at about 455 ms post stimulus), and 145 ms later, the articulation marks the completion of the whole process. Given that medial temporal lobe, the brain region for semantic processing, is prone to damage even at the prodromal stage of AD, it was hypothesized that deterioration of speech production in MCI patients might stem from breakdown of lexical retrieval.

Considering that the entire process of speech production is completed within a short period time, high temporal resolution techniques such as event-related potentials (ERPs) is poorly suited for investigation of the time course of speech production. In addition, human brain is a large-scale network, of which the function depends on dynamic interactions between spatially-distributed regions. As an objective record of nerve electrical activity in brain, electroencephalography (EEG) signal could reflect the communication between neurons [4, 5], and the analysis of brain functional network may shed further light on the intra- and inter-regional communications during the process of speech production.

To test the hypothesis, a primed picture naming task, of which the semantic relatedness between the prime character and the target picture stimulus was manipulated was carried out. Specifically, the prime and target could either be semantically related (e.g., "mouse-dog") or unrelated (e.g., "eyebrow-dog"), but in either cases, they are phonologically distinct. During task performance, EEG signals were obtained, which were further used to analyze ERP responses and to construct brain functional network. If there was severe deterioration of lexical retrieval in patients with MCI, differential priming effects might be observed behaviorally. If there was only a slight deterioration in lexical retrieval, at least some difference in their brain functional network should be found, which might indicate an alteration of information processing due to the disease.

2. Materials and methods

2.1. Participants

A total of 37 subjects, including 17 patients with MCI (10 F & 7 M) and 20 healthy controls (11 F & 9 M) participated in the present study. Among them, six (three from the MCI group and three from the normal group) were excluded for further analysis due to their excessive head movements during EEG data collection. The elderly who were diagnosed with MCI recruited from Shenzhen Luohu People's Hospital received comprehensive neuropsychological evaluations and were assigned to the group based on results of mental status examination (i.e., Montreal Cognitive Assessment, MoCA; and Mini-Mental State Examination, MMSE) and a history of cognitive decline. Participants having no history of psychiatric issues or neurological disorders were also recruited and served as healthy controls.Written informed consent was obtained from each participant prior to the experiment. Table 1 shows the demographic information of all participants.

Table 1: *Demographic information (mean and SD)*

	MCI	Normal	Statistics
Age (years)	65.7 (5.7)	66.7 (4.7)	$t = -0.63$
Gender (F/M)	10/7	11/9	$\chi^2 = 0.06$
Education (years)	11.5 (3.3)	13.9 (2.2)	$t = -2.70^{*}$
MoCA (30)	23.8 (2.3)	28.1 (1.2)	$t = -6.82^{***}$
MMSE (30)	25.2 (3.1)	28.9 (1.3)	$t = -4.66^{***}$

$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

2.2. Stimuli

Twenty-seven black and white drawings of concrete objects, selected from Snodgrass and Vanderwart picture database [6], served as picture stimuli in this study. Each picture stimulus could be named using a single Chinese phonogram consisting of a phonetic radical and a semantic radical. All picture stimuli were paired with two different types of prime character, of which the meaning was either semantically related (S+ condition, e.g., "mouse-dog") or unrelated to the picture stimuli (S- condition, e.g., "eyebrow-dog"). Psycholinguistic variables including frequency and number of strokes, object familiarity were matched across different types of primes to rule out probable confounding effects. In both cases, the prime character and the phonogram denoting the picture stimulus were not phonologically similar. By doing so, priming effects due to the ease of phonological encoding could be eliminated.

2.3. Procedure

Before the experiment commenced, all picture stimuli were initially presented to the participants in order to familiarize them with the pictures. During the experiment, the participant performed a primed picture naming task, where they were instructed to name the target picture as quickly and accurately as possible. Each trial began with a fixation cross (+) which appeared in the center of the monitor screen for 500 ms, sequentially followed by a blank screen of 300 ms. Then, the character stimulus was presented 300 ms before the onset of the picture stimulus. Presentation of visual stimuli was terminated after 2,000 ms and the next trial would begin after a blank screen presented for a random duration between 800 and 1,200 ms. The schematic drawing of the experiment is depicted in Figure 1.

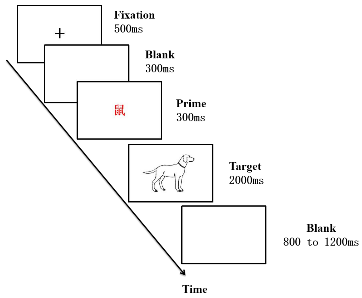

Figure 1. *Illustration of the experimental procedure in the present study*

2.4. EEG recording and ERP processing

EEG data were recorded using an EGI (Electrical Geodesics, Inc.) GES 410 system with 64 channel HydroCel GSN electrode nets. The continuous online recordings were referenced to the vertex (Cz) electrode, sampled at 1 kHz and amplified with an analog band-pass filter of 0.1 - 45 Hz. Electrode impedance was maintained below 50 kΩ. During the experiment, participants were seated in front of an LCD monitor at a distance of 60-70 cm in a sound-attenuated booth. The participants were instructed to minimize their physical movements and eye blinks throughout the experiment to reduce artifacts on the EEG recording. Oral responses were recorded and then analyzed to check whether the picture stimulus was correctly named. Errors in naming were discarded for the subsequent analysis.

In order to clean raw EEG signals, the preprocessing followed the same steps as described in several previous studies dealing with EEG data. Firstly, the continuous data were filtered by a phase-shift free high-pass of 0.5 Hz, low-pass of 30 Hz filters. Segmentation was performed from -400 to 800 ms relative to stimulus-onset. The bad channels were first identified by visual inspection and then recovered using a spherical interpolation procedure implemented in EEGLAB [7]. Trials with an incorrect response, excessive movements or eye blinks (i.e., voltage exceeding 120 μV) were automatically rejected. In addition, eye blinks were also removed by using the independent component analysis (ICA) method [8]. The remaining trials were then re-referenced to the average-mastoids reference and were used to compute the grand-averaged ERP waveform. For each participant, the ERP measurement was time-locked to the visual onset of the character stimuli.

Three components during the cognitive processing in picture naming - the N170 (160-200 ms), the P200 (200-250 ms) and the N400 component (250-380 ms) were determined from the Global Field Power (GFP) averaged across all experimental conditions and across all participants [9]. GFP along time was obtained by calculating the square root of the mean square values of all electrodes at each time point.

2.5. Network Construction

The EEG source connectivity method was used to construct brain networks [10]. The temporal dynamics of the cortical sources by solving the inverse problem were first established, and then identifying the regions of interest (ROIs). Finally, the functional connectivity between the reconstructed time series was measured. The weighted minimum norm estimate (wMNE) implemented in Brainstorm was used as inverse solution and the Destrieux atlas was used to anatomically segment the brain into 148 cortical regions [11, 12]. Synchronization between the 148 regional time series using the phase locking value (PLV) measure [10, 13] in theta frequency band (4-8 Hz) was quantified [14, 15]. This frequency band is the most relevant one when human perform cognitive task [16, 17]. The PLV ranged between 0 (no phase locking) and 1 (full synchronization).

The dynamic changes of the functional connectivity of the entire brain region, especially the large-scale language related brain region, in the process of speech production were tracked. Through the analysis of task-related ERP and GFP, the time window of different brain functional network states of cognitive processing in the task was determined. Dynamic functional connectivity matrices were then computed for three time windows using PLV correspond to the three main cognitive processing components in the experiment task.

The final networks were obtained by applying a cost threshold value to remove weak connections from the PLV matrices. In the present context, cost was defined as the ratio of the number of existing edges divided by the maximum possible number of edges in a network. Each connectivity matrix was thresholded repeatedly over a wide range of sparsity levels which the maximum threshold must assure that each network is fully connected with N = 148 nodes and the minimum threshold must assure that the brain networks have a lower global efficiency and a larger local efficiency compared to random networks with relatively the same distribution of the degrees of connectivity [18]. Consequently, we selected the small-world interval as $0.1 \leq K_{cost} \leq 0.28$ (the corresponding degree of connectivity threshold is $14.8 \leq K \leq 41.44$) for the range of sparsity levels.

2.6. Network Metrics

Clustering coefficient and characteristic path length measures were used to evaluate the topological properties of identified networks, which were interpreted as indicators of functional integration and segregation properties of the brain.

The clustering coefficient of a node in a graph quantifies how close its neighbors are to being a clique [19]. Accordingly, the average clustering coefficient of a network is considered as a direct measure of its segregation (i.e., the degree to which a network is organized into local specialized regions) [20]. The average clustering coefficient of a network can be obtained by:

$$C = \frac{1}{n}\sum_{i \in N} C_i = \frac{1}{n}\sum_{i \in N} \frac{2E_i}{K_i(K_i - 1)} \tag{1}$$

where C_i is the clustering coefficient of node i , and E_i is the number of edges in the sub-graph. Local clustering coefficient of each node is analogous to local efficiency that indicates functional segregation. The characteristic path length is a measure of how well connected a network is, which is defined as the average of the shortest path lengths between two generic vertexes [19]. A network with a low characteristic path length is characterized by short distances between any two nodes.

$$L = \frac{1}{N(N-1)} \sum_{i \neq j \in G} L_{ij} \tag{2}$$

where L_{ij} is the minimum path length between nodes i and j .

This measure is related global efficiency which depicts network integration and its overall performance for information transferring. The topological properties of brain functional network as a function of K, which is the average number of edges per vertex was investigated [21].

2.7. Data analysis

To quantify the difference in reaction time (RT) and percentage of accuracy (ACC) obtained from all participants, a two-way repeated measures ANOVA was carried out. A two-way ANOVA was conducted for the ERP components of picture naming task. The peak and mean amplitude of different ERP components was computed at electrodes points (i.e., Fz, FCz, Cz, Pz, POz) in the middle of brain. In order to assess for significant group differences in the network properties, statistical tests were performed. As data were not normally distribution, statistical differences between the two groups were assessed using Mann Whitney U Test (also known as Rank-Sum Wilcoxon test). Furthermore, the area under the curve (AUC) was calculated for each network metric [22, 23], which provided a summarized scalar for topological characterization of brain networks.

Table 2: *Mean reaction time and accuracy by condition (mean and SD)*

	MCI_S+	MCI_S-	NC_S+	NC_S-
ACC	0.95 (0.04)	0.96 (0.04)	0.99 (0.02)	0.99 (0.01)
RT(ms)	978.33 (129.56)	990.78 (154.84)	931.19 (112.89)	898.68 (128.68)

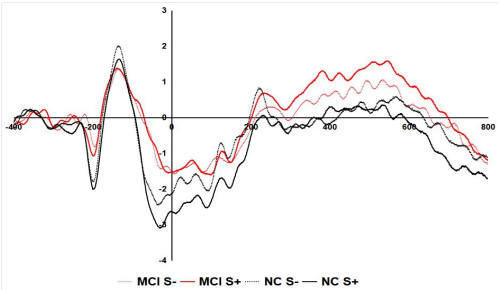

Figure 2. *Grand averaged waveforms at Cz*

3. Results

In terms of accuracy, there was a significant main effect of group [F(1,29) = 8.110, p = 0.008]. The main effect of condition [F(1,29) = 2.614, p = 0.117], however, did not reach significance. No significant interaction between these factors reached significance (p > 0.05). The ANOVA conducted on the RT revealed no significant main effect of condition [F(1,29) = 0.771, p = 0.387] or group [F(1,29) = 2.294, p = 0.141]. Neither did we observed interaction between any of these variables (p > 0.05). Table 2 shows the behavioral data including mean reaction time and accuracy by condition.

A two-way repeated measures ANOVA conducted on the N400 mean amplitude revealed no significant main effect of condition [$F(1,29) = 1.730$, $p = 0.199$] or group [$F(1,29) = 1.198$, $p = 0.283$]. Neither did we observed interaction between condition and group ($p > 0.05$). Regarding the N400 peak amplitude, there was no significant main effect of condition [$F(1,29) = 0.755$, $p = 0.392$] or group [$F(1,29) = 1.011$, $p = 0.323$]. No significant interaction between any of these variables was found either ($p > 0.05$). Grand averaged waveform at electrode site Cz is shown in Figure 2.

To better explore the differences among the network properties between two groups, the AUC for each network metric shown in Figure 4, together with the clustering coefficient and characteristic path length of network as a function of K in Figure 3 were calculated. There was a group difference with an increase in clustering coefficient ($p < 0.01$) and characteristic path length ($p < 0.01$) in MCI networks under semantically condition compared with healthy controls. The dynamics of functional networks at the time window of N400 component between two groups are shown in Figure 5.

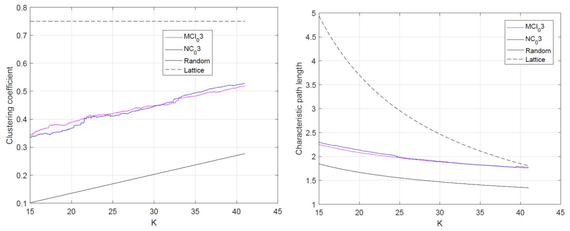

Figure 3. *Clustering coefficient and characteristic path length for healthy subjects and patients with MCI as a function for K*

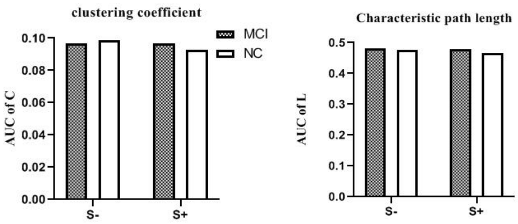

Figure 4. *The AUC of clustering coefficient and characteristic path length for healthy subjects and patients with MCI*

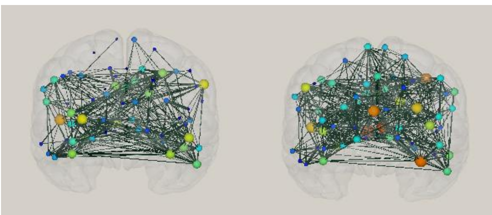

Figure 5. *Connectivity of functional network during N400 time window for healthy subjects and patients with MCI*

4. Discussion and conclusion

To our knowledge, this study is one of the very few attempts to characterize the dynamic changes over a cognitive task using both behavioral, ERP and brain network measures between MCI patients and healthy controls. In the present investigation, a primed picture naming task was adopted. The result of reaction time indicated that MCI patients did not show significant differences compared to age-matched healthy controls. This finding was in line with ERP findings, which also did not show significant differences between two groups in either condition. However, the significant main effect of group in accuracy indicated that MCI has shown a trend of impairment in lexical semantic abilities. Considering our elderly participants, pictures denoting highly familiar objects were selected. Cognitive load of this experiment should be relatively small for both MCI patients and normal elderly. At the same time, this experiment involved less cognitive load for word retrieval during speech processing. Besides, impairments that can be used to distinguish patients with MCI and their healthy counterparts are mainly in the domain of memory, while other cognitive functions are spared. However, speech impairment is not only related to word retrieval, but also requiring to conjunct words into sentences after multi-word retrieval and express the desired meaning through complete statement and dialogue, which significantly increase the cognitive load for patients with MCI. It was hypothesized that working memory might play a vital role in word retrieval during speech production as word retrieval involves the process word searching from the repository.

In order to check whether there were differences in the brain network between the two groups, the cortical functional networks were constructed from scalp signals using EEG source connectivity, and the network metrics of clustering coefficient and characteristic path length were extracted. Results revealed that networks of patients with MCI, compared to those of healthy controls, were characterized by increased clustering coefficient and characteristic path length. The longer characteristic path length and decreased global efficiency indicated that patients with MCI has a lower ability to share information between distributed regions. At the same time, one possible interpretation of an increased clustering coefficient is the compensatory mechanism that is triggered by the dysfunctional integration in the MCI brain networks. Functional segregation in the brain was the ability for specialized processing to occur with in densely interconnected groups of brain regions [24]. To some extent, functional segregation means the local information processing and the functional integration means the global information processing [14]. Hence, the results of network metrics during the word preparation indicated that global information processing of MCI patients might be deteriorated.

In sum, the present study revealed that even patients with MCI did not exhibit significant differences in reaction time and ERP responses as compared to the healthy counterparts. However, there was a significant main effect of group in accuracy, associated with a difference in functional network properties such as clustering coefficients and characteristic path length. These findings indicated that global information processing might be deteriorated during word preparation, which represented the first attempt to uncover the changes in speech production at the early stage of dementia. This could be as an evidence that deficits in lexical retrieval might have occurred even at the preclinical stage of AD.

5. Acknowledgements

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