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Resting-state EEG coupling analysis of amnestic mild cognitive impairment with type 2 diabetes mellitus by using permutation conditional mutual information

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HIGHLIGHTS

- Permutation conditional mutual information (PCMI) can describe effectively coupling.
- There are significant differences in coupling via PCMI between T2DM with/without aMCI.
- PCMI can act as an important role in distinguishing T2DM with/without aMCI.

ABSTRACT

Objective: This study was meant to explore whether the coupling strength and direction of resting-state electroencephalogram (rsEEG) could be used as an indicator to distinguish the patients of type 2 diabetes mellitus (T2DM) with or without amnestic mild cognitive impairment (aMCI).
Methods: Permutation conditional mutual information (PCMI) was used to calculate the coupling strength and direction of rsEEG signals between different brain areas of 19 aMCI and 20 normal control (NC) with T2DM on 7 frequency bands: Delta, Theta, Alpha1, Alpha2, Beta1, Beta2 and Gamma. The difference in coupling strength or direction of rsEEG between two groups was calculated. The correlation between coupling strength or direction of rsEEG and score of different neuropsychology scales were also calculated.
Results: We have demonstrated that PCMI can calculate effectively the coupling strength and directionality of EEG signals between different brain regions. The significant difference in coupling strength and directionality of EEG signals was found between the patients of aMCI and NC with T2DM on different brain regions. There also existed significant correlation between sex or age and coupling strength or coupling directionality of EEG signals between a few different brain regions from all subjects.
Conclusions: The coupling strength or directionality of EEG signals calculated by PCMI are significantly different between aMCI and NC with T2DM.
Significance: These results showed that the coupling strength or directionality of EEG signals calculated by PCMI might be used as a biomarker in distinguishing the aMCI from NC with T2DM.

1. Introduction

Diabetes is a kind of metabolic diseases characterized by high blood sugar due to insufficient secretion of insulin or cellular resistance to insulin (Shoback, 2011). Diabetes affected cognitive function and increased the risk of dementia (Gispen and Biessels, 2000; Strachan et al., 2011; Bian et al., 2014). Type 2 diabetes mellitus

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(T2DM) is a late-onset, most common type of diabetes (Kumar et al., 2005). Cognitive impairment such as learning and memory deficiency were documented in T2DM (Peila et al., 2002; Meihua et al., 2012; Huerta et al., 2013; Moran et al., 2013; Roberts et al., 2014). The T2DM may be associated with increased risk of aMCI (Ganguli et al., 2004; Busse et al., 2006; Yaffe et al., 2006; Fischer et al., 2007; Luchsinger et al., 2007; Toro et al., 2009; Shimada et al., 2010; Xu et al., 2010; Strachan et al., 2011; Tuma, 2012; Roberts et al., 2014; Bian et al., 2014; Zhang et al., 2014). Therefore, it is critical to explore effective methods to detect the aMCI of T2DM patients for the early interventions to these patients.

The resting-state EEG (rsEEG) underlies brain network activity (Steriade, 2006) and can be used for neurological evolution (Rossini et al., 2007; Schmidt et al., 2013). Recent studies have shown that rsEEG rhythms maybe a promising approach to diagnose MCI subjects (Dauwels et al., 2010b; Knyazeva et al., 2013; Babiloni et al., 2014; Wen et al., 2014). There were also several studies about the cognitive function of T2DM using EEG signals (Gerald Cooray et al., 2008; Cooray et al., 2011; Baskaran et al., 2012; Bian et al., 2014).

Due to the nature of complex characteristics in EEG signals, many methods were used to analyze the EEG signal from different perspectives (Gerald Cooray et al., 2008; Dauwels et al., 2010a; Cooray et al., 2011; Baskaran et al., 2012; Knyazeva et al., 2013; Babiloni et al., 2014; Wen et al., 2014), especially the relationship between EEG signals from different brain regions. These methods include coherence(Brassen et al., 2004; Hidasi et al., 2007; Güntekin et al., 2008; Jelles et al., 2008; Moretti et al., 2008; Dauwels et al., 2010b; Bian et al., 2014), mutual information (Dauwels et al., 2010b) and likelihood synchronization (Babiloni et al., 2006) as well as the coupling analysis (Rosenblum and Pikovsky, 2001; Rosenblum et al., 2002). Indeed the coupling analysis between different brain areas has been a focus in a number of studies in both the normal (Mizuhara and Yamaguchi, 2007; Cantero et al., 2009; Darvas et al., 2009) and the diseased brain (Rudrauf et al., 2006; Uhlhaas and Singer, 2006; Amor et al., 2009; Darvas et al., 2009).

Although the most of these methods quantified the strength of coupling or coherence, the more recent developments have been trying to estimate the coupling direction of brain rhythms at paired brain sites, these methods include transfer entropy (Schreiber, 2000), conditional mutual information, instantaneous phases of interacting oscillators (Rosenblum and Pikovsky, 2001; Rosenblum et al., 2002), state-space and phase-dynamics, and Granger causality (Lungarella and Sporns, 2006; Wang et al., 2008). Transfer entropy (Schreiber, 2000) and conditional mutual information (Paluš et al., 2001; Vejmelka and Paluš, 2008) could not calculate accurately the coupling direction between neural series (Hlavackova-Schindler et al., 2007). The instantaneous phases (Rosenblum and Pikovsky, 2001; Rosenblum et al., 2002) were sensitive to noise in the neural series and unsuitable for analyzing noisy and non-stationary EEG signals (Li et al., 2007a,b,c). State-space (Smirnov and Andrzejak, 2005) required optimal embedding parameters, but phase-dynamics (Smirnov and Bezruchko, 2003) was only used to describe strong oscillatory behavior and were sensitive to noise in the time series. Granger causality methods can be successfully applied to linear models, and only the directed transfer function of Granger causality in the above methods was often used to analyze the functional coupling direction between EEG signals from paired brain sites of cognitive impairment patients (Babiloni et al., 2008; Babiloni et al., 2009a,b; Dauwels et al., 2010b; Liu et al., 2010; Vecchio and Babiloni, 2011). However, the change in cross-prediction error based on Granger causality could not be directly applied to nonlinear time series.

Recently, the permutation conditional mutual information (PCMI), a nonlinear method, was used to estimate the coupling strength and coupling direction between two time series from mass neuronal model or neuronal populations in CA1 and CA3 in the rat hippocampal tetanus toxin model of focal epilepsy, and between spike trains (Li and Ouyang, 2010; Li et al., 2011). These studies showed that PCMI method could estimate the coupling direction and was insensitive to noise in the neural series, which was superior to the Granger causality method. Therefore, in this study, we will investigate whether or not the method also can be used to estimate the coupling strength and direction in rsEEG signals between different brain regions of T2DM patients in various frequency bands. In particular, the PCMI was applied for the analysis of the rsEEG recordings from 39 subjects, including 19 amnestic mild cognitive impairment (aMCI) and 20 normal controls (NC) with T2DM, and the difference between the coupling strength values or coupling direction indexes of aMCI and NC with T2DM were calculated. Then, the correlations between the coupling strength or directionality indexes and neuropsychological assessment scores or sex or age of all subjects were also analyzed.

2. Materials and methods

2.1. Subjects

Participants were comprised of 39 right-handed subjects who satisfied the diagnosis criteria for T2DM (Association, 2013), and they were all voluntary and the mean years were 68.95 ± 8.95 years with range from 43 to 84 years. These participants were divided into two groups: aMCI and NC. The aMCI patient group consisted of 19 subjects (12 females and 7 males; mean years of diabetes 9.19 ± 6.29 years, range from 1 to 20 years). They were recruited from patients of the Second Artillery General Hospital of PLA in China. The NC group consisted of 20 volunteers (11 females and 9 males; mean years of diabetes 13.60 ± 8.59 years, range from 1 to 30 years). They were invited to participate in the experiment from communities near the hospital through the poster. The experiment was conducted in accordance with the Declaration of Helsinki (1964). All participants in our study signed written informed consent forms authorized by the Institutional Review Board of the Second Artillery General Hospital of PLA in China prior to their participation.

2.2. Diagnostic criteria and neuropsychological measures

The symptom severity was quantified by the full-scale Chinese version of Mini-mental State Examination (MMSE) (Jia, 2010), in which the cut-off score for absence of dementia was 24 points for high school and above, 20 points for the primary, and 17 for the illiteracy participants, and Montreal Cognitive Assessment (MoCA) scores (Nasreddine et al., 2005), in which the cut-off score for absence of MCI was 26 points. In addition, other neuropsychological tests scales, which include Auditory Verbal Learning Test (AVLT) (AVLT-Immediate recall, AVLT-Delayed recall, AVLT-Delayed recognition) (Carlesimo et al., 1996), Wechsler Adult Intelligence Scale Digit Span Test (WAIS-DST) (Orsini et al., 1987), Boston Naming Test (BNT) (Gollan et al., 2007), Trail Making Test (Reitan, 1958), Verbal Fluency Test (Novelli et al., 1986), Daily Living Test (Lawton and Brody, 1969) were performed to all subjects.

The participants were all T2DM patients including aMCI and NC, whose vision and hearing were normal. They underwent MRI examination to rule out organic brain diseases. The depression that can cause cognitive impairment was excluded using DSM IV criteria for depression (Association, 1994). All patients in the two