Journal of Clinical Neuroscience xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

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

Clinical commentary

Reduced frontal activity during a verbal fluency test in fibromyalgia: A near-infrared spectroscopy study

Po-Han Chou [a,b,c,d,1], Kuo-Tung Tang [e,f,1], Yi-Hsing Chen [e,g,*], Chia-Wei Sun [c], Chih-Mao Huang [d], Der-Yuan Chen [g,h,i]

[a] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, USA
[b] Department of Psychiatry, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[c] Biomedical Optical Imaging Lab, Department of Photonics, College of Electrical and Computer Engineering, National Chiao Tung University, Hsinchu, Taiwan
[d] Department of Biological Science and Technology, National Chiao Tung University, Hsinchu, Taiwan
[e] Division of Allergy, Immunology and Rheumatology, Taichung Veterans General Hospital, Taichung, Taiwan
[f] Ph.D. Program in Translational Medicine, National Chung Hsing University, Taichung, Taiwan
[g] School of Medicine, National Yang-Ming University, Taipei, Taiwan
[h] Rheumatology and Immunology Center, China Medical University Hospital, Taichung, Taiwan
[i] School of Medicine, China Medical University, Taichung, Taiwan

A R T I C L E I N F O

Article history:
Received 6 September 2017
Accepted 5 January 2018
Available online xxxx

Keywords:
Brain dysfunction
Cognition
Fibromyalgia
Near infrared spectroscopy
NIRS

A B S T R A C T

Fibromyalgia (FM) is a complex disorder characterized by widespread chronic pain and associated sleep problems and cognitive dysfunction. However, only few studies focusing on cognitive dysfunction in FM are available so far. In the present study, we aimed to use near infrared spectroscopy (NIRS) to evaluate the brain function in FM patients subjected to a verbal fluency test (VFT). A total of 11 primary FM patients and 13 healthy individuals (HC) underwent NIRS while performing a VFT. The Fibromyalgia Impact Questionnaire (FIQ) was used to evaluate the symptom severity of FM and Beck Depression Inventory II (BDI) was used to evaluate the severities depression symptoms in study participants. Five regions of interests (ROIs) were defined: the frontal-, bilateral inferior frontal gyrus (IFG), and temporal regions. Brain activities of ROIs between the two groups were compared. In addition, we investigated the relationship between clinical symptoms and brain cortical activity in FM patients. Our results showed that there were no significant differences between HC and FM patients in age, sex, and BDI scores. We found significantly reduced brain activity over the frontal regions during a VFT in FM patients ($p = .026$). In addition, we found decreased frontal activity was associated with BDI scores ($rho = -0.755$, $p = .007$). Furthermore, there were no significant correlations between frontal activity and FIQ subscales. In conclusion, our study demonstrated a reduced frontal cortical activity during VFT in FM patients, and that NIRS could be a potential tool for evaluating brain function in FM patients in clinical settings.

1. Introduction

Fibromyalgia (FM) is a complex disorder characterized by chronic widespread pain and associated sleep problems, fatigue and cognitive dysfunction [1]. Cognitive dysfunction in FM patients remained largely unexplored until recently. Overall, cognitive dysfunctions in FM have been identified in five cognitive domains: executive function, working memory, semantic memory, episodic memory, and attention, as reviewed by Kravitz et al. [2]. Only a few neuroimaging studies have been conducted to elucidate the cognitive deficits in patients with FM. For instance, Luerding et al. found that impaired working memory was associated with gray matter loss in the anterior cingulate and medial frontal cortices [3]. Using fMRI, Seo et al. found that working memory impairment in FM patients was associated with an altered frontoparietal memory network [4]. However, only few studies were conducted to investigate this topic using near infrared spectroscopy (NIRS).

NIRS is a non-invasive neuromonitoring technique that provides a bedside measurement of oxy-hemoglobin [oxy-Hb] and deoxy-hemoglobin [deoxy-Hb] concentrations, thereby indicating regional cerebral blood volumes [9]. Based on the principle of neuro-vascular coupling also known as the hemodynamic response

* Corresponding author at: Division of Allergy, Immunology and Rheumatology, Taichung Veterans General Hospital, No. 1650, Sec. 4, Taiwan Blvd., Taichung 40705, Taiwan.

E-mail address: ysanne@vghtc.gov.tw (Y.-H. Chen).

[1] PH Chou and KT Tang contributed equally to this study.

https://doi.org/10.1016/j.jocn.2018.01.030
0967-5868/

or BOLD (Blood-Oxygenation-Level-Dependent) response, NIRS can examine functional changes of brain activity [5]. NIRS is advantageous in demonstrating the spatio-temporal characteristics of neural activity in the bilateral frontotemporal regions; it shows strong correlations with brain fMRI signals [6]. To the best of our knowledge, only one study conducted by Uceyler and colleagues investigated the brain activity during verbal fluency test (VFT) in FM patients using NIRS [7]. However, these authors did not examine the relationship between the severity of FM symptoms and brain function. Therefore, the relationship between cognitive dysfunction and symptom severity in FM remains unclear.

The aim of this study was to examine the relationship between brain activity during VFT and the severity of symptoms in FM. Based on the results of previous neuroimaging studies showing the role of frontotemporal lobe dysfunction in FM patients [4,8,9], we hypothesize that FM patients are characterized by a reduced activity in the frontal cortex and that this reduction is associated with the severity of FM symptoms.

2. Methods

2.1. Study participants

The study enrolled 11 primary FM outpatients (1 man and 10 women) from the Division of Allergy, Immunology and Rheumatology at the Taichung Veterans General Hospital. FM was diagnosed according to the 1990 criteria of the American College of Rheumatology [10]. Inclusion criteria were: patient age $\geq$ 18 years; exclusion of other potential differential diagnoses (e.g. rheumatologic, orthopedic); absence of clinically relevant psychiatric disorders, as determined using the Mini International Neuropsychiatric Interview (MINI) [11]; and the willingness to participate in all tests during the study.

Thirteen healthy individuals (HC) (1 man and 12 women) were recruited as control subjects and screened using the MINI. All study participants were right-handed, which was defined by a score > 70 points in the Edinburgh Inventory [12]. Subjects with a personal history of any axis I or II disorder, a history of substance abuse or dependence, mental retardation, neurological disorder, or a medical condition that could have affected the structure or the function of the brain were excluded from the study. This study complied with the Declaration of Helsinki, and was approved by the Institutional Review Board of Taichung Veterans General Hospital (approval No. CF15045 and No. CF13044). All participants received a complete explanation of the study and provided a written informed consent.

2.2. Clinical measurements

2.2.1. Fibromyalgia Impact Questionnaire

The Fibromyalgia Impact Questionnaire (FIQ) was translated to Chinese, and used to determine FM-associated symptoms, daily impairment, and the overall well-being of the participants in the week preceding the study [13]. The maximum FIQ score is 100. The first item of FIQ comprised of 11 questions. These 11 questions were scored and averaged to yield a physical impairment subscale score.

2.2.2. Beck Depression Inventory-II

Depression was assessed using the Chinese version of Beck Depression Inventory II (BDI-II) [14].The BDI-II consists of 21 questions that are designed to assess the severity of common depressive symptoms. For each item, participants are required to select an item on the point scale (from 0 to 3) that best describes how they felt in the two weeks preceding the evaluation. Total scores on this measure ranged between 0 and 63, with higher scores indicating higher levels of depression.

2.3. Cognitive activation task

The patients completed a 160-s block-design VFT (letter version). Details of the VFT can be found in our previous work [15–17]. In brief, each 160-s block comprises of three different time periods: a 30-s pre-task period, a 60-s task period, and a 70-s post-task period. In the pre- and post-task periods, patients were instructed to fix their gaze at the center of the screen and repeatedly count from one to five to control and remove task-related motion artefacts. During the 60-s task period of the VFT, the participants were instructed to pronounce as many words as possible that start with a phonological syllable, presented as an audible instruction by a computer. The task period comprised three continuous 20-s sub-periods, which were initiated by a single Chinese phonetic symbol selected from nine possible options (first, /ㄅ(b)/, /ㄆ(p)/, or /ㄉ(d)/; second, /ㄊ(t)/, /ㄌ(l)/, or /ㄋ(n)/; third, /ㄇ(m)/, /ㄈ(f)/, or /ㄘ(dz)/). We then recorded the total number of correct words generated as an index of VFT performance.

2.4. NIRS instrument

We used a 52-channel NIRS instrument (ETG-4000; Hitachi Medical Co., Tokyo, Japan) to measure changes in [oxy-Hb]. The NIRS probe attachments are thermoplastic 3×11 shells set with 52 channels (Fig. 1). Other details regarding the setting of each channel, the principles, data sampling, and artefact processing can be found in our previous works [18,19]. According to the LONI Probabilistic Brain Atlas (LPBA) [20], NIRS channels were anatomically labelled only after the LPBA region of highest probability was determined [15,16,21]. We used the mean changes in [oxy-Hb] measured during the VFT as indices of brain cortical activity because levels of [oxy-Hb] show stronger correlations with fMRI blood-oxygenation level-dependent signals than those of [deoxy-Hb] [6].

2.5. Region of interest

Considering that channels on the upper area of the head, covered by hair, were subjected to artefacts, five regions of interest (ROIs) were defined (Fig. 1C) [18]: the frontal, bilateral inferior frontal gyrus (IFG), and bilateral temporal regions. The frontal region (located approximately in the bilateral fronto-polar and dorsolateral prefrontal cortical regions was defined as the region covered by channels 25–28, 36–38, and 46–49; the left IFG region as the region covered by channels 29, 39–40, and 50; the right IFG region as the region covered by channels 24, 34–35, and 45; the left temporal region as the region covered by channels 41–42 and 51–52; and the right temporal region as the region covered by channels 32–33 and 43–44. The average value of mean [oxy-Hb] changes in the ROI was designated as the representative measure for data analysis.

2.6. Statistical analysis

Because of small sample size and that some variables were not normally distributed (see supplementary material for details), we used non-parametric tests such as Mann-Whitney U tests to investigate the differences of variables between the two groups and Spearman's rank correlation coefficients to examine the relationship between brain activity and clinical variables. First, basic