ELSEVIER

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring ■ (2016) 1-8

Alzheimer's & Dementia

Diagnostic Assessment & Prognosis

Random forest to differentiate dementia with Lewy bodies from Alzheimer's disease

Meenakshi Dauwan[a,b,*,1], Jessica J. van der Zande[c,1], Edwin van Dellen[a,b,c], Iris E. C. Sommer[b], Philip Scheltens[c], Afina W. Lemstra[c], Cornelis J. Stam[a]

[a]*Department of Clinical Neurophysiology and MEG Center, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands*
[b]*Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands*
[c]*Alzheimer Center and Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands*

Abstract

Introduction: The aim of this study was to build a random forest classifier to improve the diagnostic accuracy in differentiating dementia with Lewy bodies (DLB) from Alzheimer's disease (AD) and to quantify the relevance of multimodal diagnostic measures, with a focus on electroencephalography (EEG).

Methods: A total of 66 DLB, 66 AD patients, and 66 controls were selected from the Amsterdam Dementia Cohort. Quantitative EEG (qEEG) measures were combined with clinical, neuropsychological, visual EEG, neuro-imaging, and cerebrospinal fluid (CSF) data. Variable importance scores were calculated per diagnostic variable.

Results: For discrimination between DLB and AD, the diagnostic accuracy of the classifier was 86%. Beta power was identified as the single most important discriminating variable. qEEG increased the accuracy of the other multimodal diagnostic data with almost 10%.

Discussion: Quantitative EEG has a higher discriminating value than the combination of the other multimodal variables in the differentiation between DLB and AD.

Keywords: Alzheimer's disease; Dementia with Lewy bodies; EEG; Random forest; Diagnostic accuracy; Beta power; Machine learning

1. Background

Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) are the two most common forms of dementia in the aging population [1,2]. DLB and AD have several overlapping characteristics, making differential diagnosis in clinical practice at times difficult [3]. Compared to AD, consensus criteria [1] in DLB have moderate sensitivity [4,5]. Accurate diagnosis of DLB and AD is essential for patient guidance and appliance of possible early treatment and prevention strategies [6]. Therefore, disease-specific biomarkers from cerebrospinal fluid (CSF) and neuro-imaging are increasingly used, but these diagnostic tests can be costly and are not always available [5,7]. Furthermore, the frequent presence of concomitant AD pathology in DLB patients renders amyloid markers and magnetic resonance imaging (MRI) less discriminative [5,8]. In contrast, electroencephalography (EEG) has been proposed as a low cost and readily available diagnostic tool to distinguish between DLB and AD [9,10]. At present, in a clinical setting, data from patient history and above-mentioned diagnostic tests are weighted differently in each individual patient to make a diagnosis [11]. The exact contribution of the (combinations of) EEG and other diagnostic tests to the differential diagnosis of DLB and AD remains unclear.

The authors declare no conflicts of interest.

[1]Both authors contributed equally to the study.

*Corresponding author. Tel.: +31-88-75-57468; Fax: ■■■.
E-mail address: m.dauwan-3@umcutrecht.nl

http://dx.doi.org/10.1016/j.dadm.2016.07.003

Automated classification algorithms can directly provide the most relevant diagnostic variables and estimate their relative importance in classifying cognitive impairment, which can improve diagnostic efficiency [12,13]. Ensemble-learning methods construct automated classification algorithms that can learn from and predict data by building a model in the form of input-output relationships of variables (i.e., features in classification algorithms) [14]. Random forest is one such algorithm, developed by L. Breiman, and based on the principle of decision-tree learning [15]. In the field of dementia, ensemble-learning methods have mainly been studied to classify patients with AD [13], whereas very little evidence is available on the automated discrimination between DLB and AD [12] or on the combination of different diagnostic modalities in an automated classifier.

This study aimed to build a random forest classifier to discriminate between DLB, AD, and controls and to quantify the importance of (combinations of) different types of diagnostic features (i.e., clinical, neuropsychological, EEG, CSF, and neuro-imaging data), with a specific focus on the role of EEG.

2. Methods

2.1. Study population

A total of 66 probable DLB patients, 66 probable AD patients, and 66 subjects with subjective cognitive decline (SCD) were selected from the Amsterdam Dementia Cohort [11]. The groups were matched on group level for age and gender. All subjects were referred to the Alzheimer Center of the VU University Medical Center (VUmc) in Amsterdam, The Netherlands, between September 2003 and June 2010. Standardized dementia diagnostic work-up included neuropsychological assessment, lumbar puncture, brain MRI, and resting-state EEG. All subjects gave written informed consent for storage and use of their clinical data for research purposes. The Medical Ethics Committee of the VUmc approved this study. A clinical diagnosis and treatment plan were made by consensus in a weekly multidisciplinary meeting [11]. Probable AD was diagnosed according to the NINCDS-ADRDA criteria [2], and probable DLB was diagnosed according to consensus guidelines [1]. Subjects were labeled as SCD when they experienced and presented with cognitive complaints, but diagnostic work-up was not abnormal and no other neurological or psychiatric disorder known to cause cognitive problems could be diagnosed [11]. These subjects were included as controls.

The EEG-data set of the present study population has been previously analyzed focusing on functional and directed connectivity and network topology in DLB and AD [16,17].

2.2. Feature selection

All the non-EEG features (Table 1) for the classification algorithm were manually selected from the diagnostic work-up based on availability, and their correspondence with the clinical criteria of DLB and AD [1,2].

2.2.1. Clinical features

Visual hallucinations were assessed with the Neuropsychiatric Inventory (NPI) [18]. Cognitive functions were assessed using a standardized test battery [11]. From this, the Mini-Mental State Examination (MMSE) was used as a measure of global cognitive function [19], Trail Making Test part A (TMT-A) as a measure of motor speed [20], the Visual Association Test (VAT) as a measure of episodic memory [21], and the forward and backward condition of the Digit Span as a measure of attention [22].

2.2.2. Biomarkers

CSF was collected by lumbar puncture [11]. Amyloid-β 1–42 ($A\beta_{42}$), total tau, phosphorylated tau (p-tau), and a ratio of tau to $A\beta_{42}$ were included as features [23]. From neuroimaging, medial temporal lobe atrophy, global cortical atrophy, and white-matter hyperintensities on MRI were included as features [11].

2.2.3. EEG recordings

As part of the diagnostic work-up, all subjects underwent a 20-minute no-task, resting-state EEG recording with OSG digital equipment (Brainlab; OSG B.V. Belgium), according to the international 10–20 system [17].

EEGs of all subjects were rated according to a standard visual rating scheme [24]. The visual rating includes the severity of EEG abnormalities on a 4-point rating scale, and the presence of focal, diffuse, and epileptiform abnormalities [11,24]. In addition, all EEGs were assessed for the presence of frontal intermittent rhythmic delta activity [9,10].

Subsequently, four artifact-free epochs, recorded in an awake state with eyes closed, were visually selected for each subject. Data were converted to American Standard Code for Information Interchange (ASCII) format, and four epochs of 4096 samples per subject (i.e., approximately 4×8 second EEG data per subject, sufficient to perform qEEG analyses [25]) were loaded into the BrainWave software for further analysis (BrainWave, version 0.9.152.2.17, C.J. Stam; available for download at http://home.kpn.nl/stam7883/brainwave.html).

The machine learning module of BrainWave was used to create a data file containing all the qEEG features shown in Table 1. Phase transfer entropy (PTE) was used as a measure for effective connectivity between EEG channels. PTE measures the strength and direction of phase-based functional connectivity between interacting oscillations [26]. In addition, minimum spanning tree (MST) measures (i.e., highest degree, leaf number, and tree hierarchy) were used as a representation of functional network topology. MST is a unique acyclic subnetwork that connects all nodes in a network such that only the strongest connections in the network are included without forming loops [27].