A Mahalanobis Distance Based Approach towards the Reliable Detection of Geriatric Depression Symptoms Co-existing with Cognitive Decline

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Abstract. Geriatric depression is a highly frequent medical condition that influences independent living and social life of senior citizens. It also affects their medical condition due to reduced commitment to the appropriate treatment. Coexistence of depressive symptoms in Mild Cognitive Impairment (MCI) and lack of objective tools towards their reliable distinction from neurodegeneration, motivated this study to propose a computerized approach of depression recognition. Resting state electroencephalographic data of both rhythmic activity and synchronization features were extracted and the Mahalanobis Distance (MD) classifier was adopted in order to differentiate 33 depressive patients from an equal number of age-matched controls. Both groups demonstrated cognitive decline within the context of MCI. The promising results (89.39% overall classification accuracy, 93.94% sensitivity and 84.85% specificity) imply that combination of neurophysiological (EEG) and neuropsychological tools with pattern recognition techniques may provide an integrative diagnosis of geriatric depression with high accuracy.

Keywords: Geriatric Depression, Electroencephalography, Mild Cognitive Impairment, Mahalanobis Distance Classifier, Wavelet Entropy, Neuropsychological Estimation.

1 Introduction

The overall prevalence rate of depressive disorders among the elderly varies between 10% and 20% [2]. According to projections by the World Health Organization (WHO) depression will be the leading cause of Disability Adjusted Life Years (DALYs) lost in high income countries in 2030 [3]. Contrary to popular belief, depression is not a natural part of aging and often reversible with prompt and

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appropriate treatment [4]. However, if left untreated, it leads not only to considerable influences on functional impairment and disability [5], [6], but also to increased cardiovascular diseases, mortality risks and a decreased quality of life, along with increased health care utilization and medical costs. Hence, early detection and treatment is important in chronically ill elderly persons, thereby preventing a downward spiral [7], [8].

Depression is highly prevalent among individuals with dementia of any degree and any type [9]. Depressive symptoms are also common in mild cognitive impairment (MCI) and appear to hasten conversion from MCI to clinical Alzheimer 's disease (AD) [10], [11]. Depression, subcortical dementia, and normal aging may all have similar neurobehavioral manifestations, a fact that makes the differentiation between depression and dementia in the elderly extremely complicated [2]. Still controversial is whether depression prior to dementia represents a risk factor for dementia or a prodromal feature of dementia and the most likely scenario seems that depression can be both an early or midlife risk factor for dementia and also an early sign of incipient dementia. For instance, in a late stage of dementia depression could be due to specific structural or biochemical changes in the brain [9]. Furthermore, maturational changes in the brain may increase vulnerability for the development of late-life depression [13] while in late-onset depression, structural imaging studies point not only to changes in deep frontal white matter but also to structural changes in the hippocampus and prefrontal cortex [10]. These alterations including connections with the limbic system have been hypothesized to increase vulnerability for depression and contribute to the manifestation of declines in cognition and subsequent executive dysfunction associated with late-life depression [13]. The widespread structural brain changes mentioned include structures which are affected by AD pathology too [11] rendering the diagnosis of depression in the context of dementia complicated [12].

A closer look at the relationship between depression and dementia development illustrates complexity of this relationship. For instance, cognitively intact elderly individuals who develop depression are at increased risk of subsequent MCI [14]. In fact in cognitively intact subjects, symptoms of depressive mood were related to AD development [15]. In a different study it is demonstrated that although not all patients with MCI develop dementia, in those who do, those who present with depression as well, are at more than twice the risk of developing AD (as those without depression) [16]. Though it is not clear yet whether depression is a cause or a consequence of cognitive impairment in older populations, it has been found nevertheless that there is indeed an association between MCI in specific and depression, which in turn leads to a worse clinical outcome of depression (and potentially faster cognitive decline) [17]. Depression, however, has also been found to be a risk factor for AD in individuals without cognitive impairment [18]. In a review of relevant studies, it was concluded that depressive symptoms are not related to progression from MCI to dementia [15], while it has not been precluded that depression may contribute to cognitive deficits in the elderly. If depressive symptoms in certain MCI cases are indeed related to a different etiology, separate from a neurodegenerative mechanism [15] that remains to be examined.

The role of depression in dementia is without doubt complicated. Depression in older individuals may mimic or exacerbate symptoms of other progressive dementing conditions, thus making differential diagnosis difficult [19]. Despite the large

literature and findings on the connections between depression and dementia (whether that be preclinical, MCI or AD), there is no integrated method to strengthen the already existing approaches and lead to more solid differential diagnoses. Bearing that in mind, the current study sought to set the basis for a stronger diagnosis method. Therefore, it is clear that improved diagnostic tools are essential to further clarify the relationship between depressive symptomatology and dementia, and mainly MCI, in older populations. Depressive symptomatology needs to be examined through clinical diagnosis, supported by neuropsychological assessment, adding to data from neurophysiological measures. Neuropsychological assessment of an individual with clinical depression is expected to underline impairments typically seen in cognitive faculties such as attention, memory components such as short-term recognition and recall or long-term episodic and semantic memory, abstraction and executive functions, language, motor skills as well as visuospatial functions [19], or show slowed mental processing [20]. Neuropsychological assessment will allow for the brain-behavior relationship to be explored and to further develop inferences on the neuroanatomical substrates of the disease [19].

Several research questions arise regarding geriatric depression and pathological aging due to neurodegeneration. Can MCI develop in all patients with depressive symptomatology? And if yes, how soon, and to what extend? What changes in the brain due to aging may facilitate this process of MCI development, with or without depressive symptoms present? Can MCI along with depression be viewed as a stronger predictor of AD development than MCI or depression alone? Which neuropsychological measures in particular may be useful in the differential diagnosis of depression from early dementia types such as MCI? If they are used parallel to neurophysiological measures such as EEG, will their predictive value increase, and will this combination of measures assist in differentiation and further treatment?

Our hypothesis is that a large portion of MCI patients suffer simultaneously from geriatric depression. The coexistence of depression reduces their commitment to interventions regarding dementia and prompts them to self-occlusion and further deterioration. Despite depression diagnosis is of vital importance, there is not a plethora of objective and reliable diagnostic tools. So, it is mainly supported on subjective questionnaires and to the therapist's experience. Aiming to provide a robust and simple computerized tool that may be used to clinical practice , we propose the use of resting state EEG data and a pattern recognition technique towards the detection of the depressive symptoms.

2 Methodology

The study employed 66 (six male) elderly participants recruited from day care centers and the Greek Association of Alzheimer's Disease and Related Disorders. They were subdivided equally in two groups of 33 participants / group. The first group consisted of elderly participants diagnosed with geriatric depression and memory loss or minor cognitive deficits like Mild Cognitive Impairment. The second group consisted of elderly participants free of depressive symptoms. Both groups were matched regarding their age and cognitive status. Inclusion criteria were age of 58 and older,

approval to participate from their personal doctor and signing the informed consent. Exclusion criteria were dementia diagnosis, drug or substance abuse, recent usage of cholinesterase inhibitors or anti-depressive drugs (less than 3 months), severe neurological disorder due to ischemic attack and severe mobility problems. This study was part of the Long Lasting Memories EU FP7 funded program which aimed to promote healthy and independent aging through cognitive and/or physical training. Prior to their participation they were informed about the research procedure and aims. Then, they had the chance to ask anything they wanted regarding the study and signed an informed consent form. The study was approved by the local ethical committee. Group details are given in Table 1.

Table 1. Group details regarding mean age, depression and cognitive status

Group	Age	GDS	MMSE	MoCA
Depression	69.818	7 ± 1.62	25.455 ± 2.762	22.485 ± 3.589
Control	70.333	1.667 ± 1.574	25.727 ± 1.892	22.273 ± 2.798

The neuropsychological examination focused on the presence of cognitive impairment relevant to MCI and to depression. The Short Form Geriatric Depression Scale (GDS), which consists of 15 questions, was used for the depression identification. The GDS is a tool with validity and reliability supported through both clinical practice and research. The participant's cognitive status was assessed through the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) test. The MMSE is commonly used for memory complaints of memory problem, since it offers a general screening tool for a number of different mental abilities including memory, attention and language. It is often combined with the MoCA examination which is a rapid screening instrument for mild cognitive dysfunction assessing different cognitive domains. Verbal memory was assessed through the California Verbal Learning Task (CVLT). Conclusions regarding psychomotor speed and executive control function were derived by Trail-Making Test Part A and B and working memory was assessed with Digit Span Task. The ability to perform daily self-care activities was measured by the Instrumental Activities of Daily Living (IADL) test. Finally, the WHOQOL-BREF, a shorter version of the World Health Organization Quality Of Life Instrument, was used to estimate the subjective quality of life including physical, psychological, social and environmental domains.

Neurophysiological data acquisition was employed in order to provide a direct window of mature brain functioning enabling thus the reliable detection and quantification of cognitive decline and brain deviations due to depression symptoms. Participants were sat in a comfortable armed chair during the neurophysiological examination, performed through a Nihon Kohden JE-207A device equipped with 57 active electrodes attached on a cap fitted to the participant's scalp. Electrode impedances were kept lower than 2 KΩ. Reference electrodes were positioned at the mastoids. The sampling rate was set at the 500 Hz. The data acquisition procedure is visualized in Figure 1. The experimental procedure involved resting state EEG data

acquisition with eyes closed. The data acquisition lasted for approximately four minutes and was part of a longer neurophysiological examination within the context of the Long Lasting Memories screening procedure [23].

The pre-processing was performed through the MATLAB programming environment and the EEGLAB graphic user interface. The EEG signals serve as an input to the Independent Component Analysis (ICA) algorithm. The ICA algorithm computes the source estimations that are hypothesized to produce the input EEG signals. Thanks to this kind of analysis, noise sources (e.g. eye blinks, muscle artifacts, heart modulation) are recognized and rejected. After the removal of the noisy source components, the whole EEG data were visually inspected by two experts in order to identify data segments that are temporally contaminated with noise. These short time segments are manually rejected. Then, a continuous interval of 20 seconds of artifact-free EEG data was selected for the feature extraction phase.

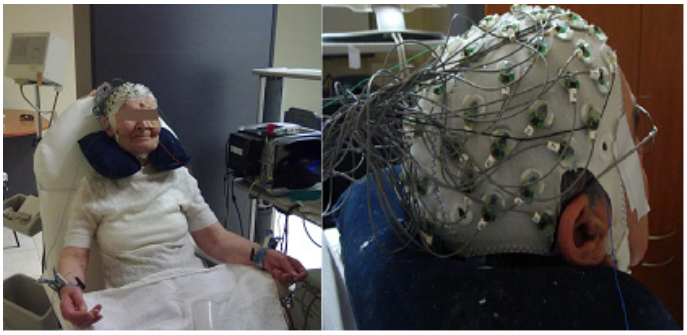

Fig. 1. Visualization of the data acquisition equipment

The 20 seconds EEG data were divided in 150 windows of 128 milliseconds duration. The Discrete Wavelet transform (DWT) at periodization mode was then employed in order to compute the wavelet coefficients for each time window. The duration of the time window was set at 128 ms, which was the minimum time duration that needed for the computation of one wavelet coefficient correspond to the delta frequency band. The DWT scheme performs iterative time-frequency decomposition (first layer of Figure 2) in order to extract the activity of each frequency band with optimal resolution through recursive filtering (second layer of Figure 2) [24]. The wavelet coefficients that correspond to the delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-16 Hz), beta (16-32 Hz) and gamma (32-62 Hz) band are used in order to compute the energy (Ej, j=1…5) of each one of the aforementioned frequency bands, through the following type:

$$E_j = \sum_{j=1}^{5} \left| C_j \right|^2 , E_{tot} = \sum_{j=1}^{5} E_j \quad (1).$$

Then, the relative energy of each frequency band is computed (band's contribution to the total EEG energy). Finally, the synchronization degree between the energy

distributions of each electrode pair is extracted (third layer of Figure 2) according to the following type:

$$S_{\mathrm{WT}}(p|q) = \sum_{j<0} p_j \cdot \ln\left[\frac{p_j}{q_j}\right], \quad (2),$$

where p and q the energy distributions of the two electrodes forming the electrode pair under consideration.

The electrodes were divided according to their topological distributions in 12 categories: prefrontal, frontal, central, frontocentral, frontotemporal, temporal, anteriofrontal, parietal, parietotemporal, occipital, parietooccipital and centroparietal. So, except from the synchronization features, mean energy values for each one topological cluster were also computed and served as additional features. Therefore, the pool of features consists of both synchronization and energy characteristics.

The huge amount of features extracted from the relative wavelet entropy analysis (57 × 57 = 3249 features) pose the issue of feature selection. Therefore, a strict threshold was defined. The threshold absolute value was set at 0.06, allowing both synchronization and desynchronization features to be selected. The strict threshold resulted in the selection of three synchronization features and seven desynchronization features.

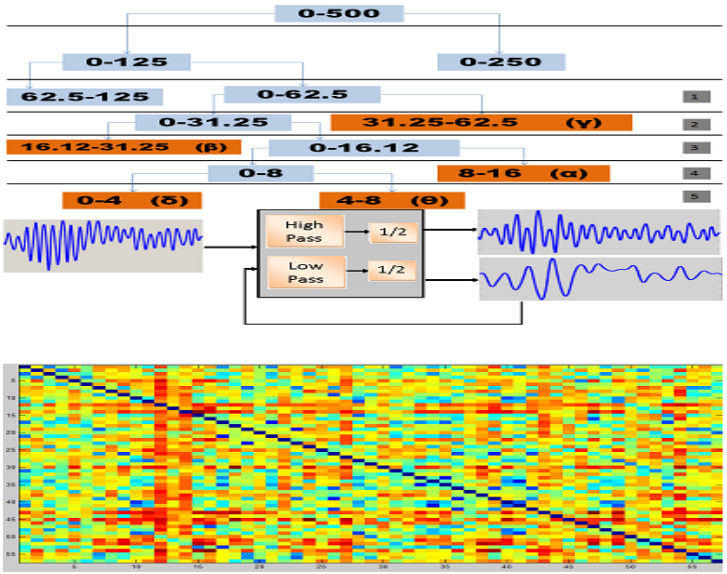

Fig. 2. Visualization of the iterative five-step frequency decomposition scheme adopted by the Discrete Wavelet Transform (DWT) (layer 1); the recursive filtering framework used for the extraction of the activity of each frequency band under consideration (delta, theta, alpha, beta and gamma) (layer 2); and the Relative Wavelet Entropy (RWE) synchronization matrix (layer 3)

The Mahalanobis Distance (MD) classifier was employed [24]. It is a simple yet robust distance based classifier, which is defined by the following formula:

$$D_M(x) = \sqrt{(x-\mu)^T S^{-1}(x-\mu)} \tag{3}$$

Let assume that we have **N** features that would be employed for the classification scheme. The average value (centroid) of each feature forms the N-dimensional μ vector. **S** denotes the covariance matrix and the **x** variable denotes each instance (one value from each feature corresponding to a single participant) as defined in (4):

$$x = (x_1, x_2, \ldots, xN)^T,\ \mu = (\mu_1, \mu_2, \ldots, \mu N)^T \tag{4}$$

3 Results

The huge amount of the features extracted from both the rhythmic activity computation and the synchronization evaluation were submitted to statistical analysis through Student t-test. The statistical significance threshold was set at $p < 0.05$. Bonferroni correction was also used. This procedure served as a pre-processing feature evaluation in order to detect the most important features that could differentiate the two groups. Regarding the synchronization features, the most prominent differences were found among the following electrode pairs: F8-Afz, Fz-FC3, P2-F7, Af4-C2, CP1-Af4, FC2-Af4, C2-Af4, CPz-FC3 and F7-P2.

Rhythmic activity energy features were also statistically significant. High frequency oscillations occurring within the gamma band differentiated the two groups on anteriofrontal and frontocentral locations. Beta band features were significant on central and parietal positions. No feature was highly statistical significant within the alpha frequency band. Theta energy features from parietooccipital and prefrontal areas were also used. Features extracted from the delta frequency band proved to best differentiate the two groups on several areas like centroparietal, parietooccipital, occipital, central, frontocentral and temporal locations. These features (10 from the synchronization analysis and 11 from rhythmic activity computation) were used in order to discriminate neurophysiological alterations between depressed and non-depressed patients that also suffer from subjective or mild cognitive impairment.

The classification rates for the two groups (depressive & controls) and the overall accuracy rate is depicted in Figure 3. The number of features used was 21. The classification accuracy for the patients suffering from depression was 93.94% (31/33) and 84.85% (28/33) for the age and cognitive status matched control group. So, the overall accuracy rate reached the 89.39%. According to these results the number of true positives is 31/33, false positives are 5/33, true negatives are 28/33 and false negatives are 2/33.

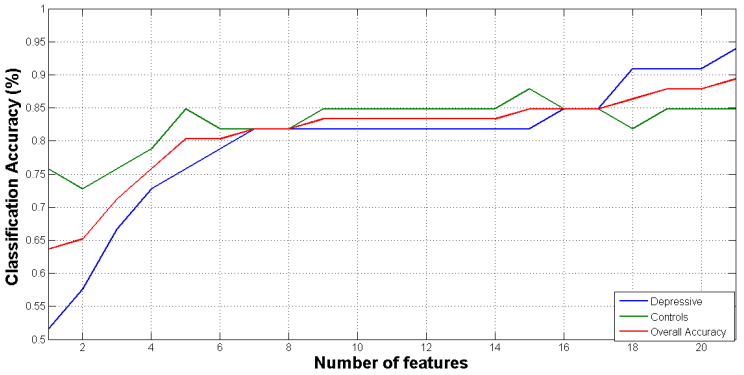

Fig. 3. Classification accuracy of the Mahalanobis Distance (MD) based classifier

4 Discussion

The proposed Mahalanobis Distance (MD) based tool is one of the early attempts aiming to detect depression symptoms that co-exist with cognitive deficits characterizing pathological aging. Therefore, the problem's difficulty is much more complex since brain alterations occur both due to depression and neurodegeneration. Its clinical utility would be of major importance, since it would be used as a screening tool prior to non-pharmacological interventions aiming to delay or prevent dementia onset. Therapy dropout ratings are mainly attributed to depressive patients due to less commitment and reduced socialization. Therefore, such a system would recognize depressive participants at high risk of not finalizing the program (therapy wise) and special care would be given towards their encouragement to complete it and towards providing them with positive feedback. Towards this direction, it is important to introduce a multi-modal screening tool that processes neurophysiological and neuropsychological data, self reports and clinical diagnosis in order to provide a definitive depression diagnosis through a data mining tool.

Despite the promising results, there are still study limitations such as the lack of gender balanced participants. The sampled population of this study did not have a clear cut diagnosis of clinical depression (only depressive symptomatology), making further comparisons of groups more difficult. For instance, the results of the short form GDS are not necessarily suggestive of depressive symptomatology, an issue of concern in the current study. Moreover, type of depressive symptomatology was not examined, such as anxiety versus depressed mood types of symptoms, which appear to present differently in the presence of cognitive difficulties. Moreover, the sample size is relatively small in order to extract normative ratings that could establish a standardized diagnostic tool.

In future research, clinical depression should be diagnosed by means of a full clinical interview, fortified with the inclusion of more detailed self report measures. Furthermore, more detailed neuropsychological assessment should be performed to assist in the differentiation between dementia and depression, and examine further the

etiology. Repeat testing will provide valuable information on depression and dementia features alike. To summarize, this study proposes a novel recognition scheme aiming to form a screening tool in the under-studied field of geriatric depression occurring simultaneously with cognitive neurodegeneration. Potential applications except from the definitive diagnosis of depression would be the personalized selection of cognitive and physical dementia-related intervention treatment and selection of an appropriate way of providing emotional feedback to elderly in order to increase their self esteem, socialization and independent living.

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