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Improved detection of amnestic MCI by means of discriminative vector quantization of single-trial cognitive ERP responses

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HIGHLIGHTS

- Single trial ERPs reveal cognitive impairments better than the averaged response.
- Using a semantically defined codebook, response dynamics can be described and compared in an intelligible way.
- This codebook representation contributes significantly to the reliable detection of cognitive decline.

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ABSTRACT

Cognitive event-related potentials (ERPs) are widely employed in the study of dementive disorders. The morphology of averaged response is known to be under the influence of neurodegenerative processes and exploited for diagnostic purposes. This work is built over the idea that there is additional information in the dynamics of single-trial responses.

We introduce a novel way to detect mild cognitive impairment (MCI) from the recordings of auditory ERP responses. Using single trial responses from a cohort of 25 amnestic MCI patients and a group of age-matched controls, we suggest a descriptor capable of encapsulating single-trial (ST) response dynamics for the benefit of early diagnosis.

A customized vector quantization (VQ) scheme is first employed to summarize the overall set of ST-responses by means of a small-sized codebook of brain waves that is semantically organized. Each ST-response is then treated as a trajectory that can be encoded as a sequence of code vectors. A subject's set of responses is consequently represented as a histogram of activated code vectors. Discriminating MCI patients from healthy controls is based on the deduced response profiles and carried out by means of a standard machine learning procedure.

The novel response representation was found to improve significantly MCI detection with respect to the standard alternative representation obtained via ensemble averaging (13% in terms of sensitivity and 6% in terms of specificity). Hence, the role of cognitive ERPs as biomarker for MCI can be enhanced by adopting the delicate description of our VQ scheme.

1. Introduction

Alzheimer's disease (AD) is a neuro-degenerative disorder that is characterized by a gradual deterioration in various cognitive processes, functional abilities, and behavior. Current therapeutic schemes are not effective in treating the early manifestations of dementia but future strategies may provide some opportunities for managing the disease while the patient's cognitive abilities are relatively preserved (Babiloni et al., 2006). The distinction between normal aging and incipient-prodromal AD is therefore of great importance today and any tactic for the reliable clinical assessment finds application as a potential marker of early disease presence, progression and response to therapy.

Mild cognitive impairment (MCI) is described as the transitional stage between normal cognitive changes of aging and the cognitive decline caused by AD. It has recently attracted clinical and research interest, since MCI patients are at increased risk for progressing in to AD (Galvin et al., 2005). The timely identification of those subjects who are about to convert to AD offers the opportunity of therapeutic intervention at the early stages of the involved neurodegenerative processes, thereby enhancing response to therapy.

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Recently the diagnosis of MCI has been refined and the current diagnostic typology includes nonamnestic and multiple cognitive domain subtypes (Winblad et al., 2004). Amnestic MCI has been studied intensively because these patients have six time higher risk of converting to AD relative to age-matched controls (Petersen et al., 1999) and have neuropathology similar to early AD.

Cognitive event-related potentials (ERPs) are widely employed in the study of dementive disorders (Frodl et al., 2002; Polich and Corey-Bloom, 2005; Papaliagkas et al., 2008; Lai et al., 2010; Papaliagkas et al., 2011). The non-invasive character of ERP measurements, the resulting easy-to-interpret indices, and their independence from cultural and educational factors are among the most important advantages of this approach. An "oddball" stimulus paradigm is most often employed to elicit auditory event related potentials (AERPs) and, by averaging the responses to target tones, the two major deflections known as N200 and P300 are restored and evaluated (Golob et al., 2001). P300 is an endogeneous brain response that occurs as a positive deflection approximately 300 ms after the onset of stimulus whenever a subject detect an informative task-relevant stimulus (Polich and Corey-Bloom, 2005). The N200 is a faster component that reflects cognitive processes of stimulus evaluation, selective attention and conscious discrimination (Patel and Azzam, 2005). The precise neurophysiological origin of these two components remains rather elusive and the relevant explorations has led to further subdivisions (Polich, 2007). However, latency and amplitude measurements of these two deflections are considered to suffice for assessing cognitive decline (Muscoso et al., 2006; Bennys et al., 2007; Golob et al., 2007; Caravaglios et al., 2008).

Deviating from the conventional approach to analyzing ERPs by extracting morphological characteristics (peak amplitude/latencies) from the averaged response, we aimed for a thorough analysis of single-trial responses by analyzing the event-related temporal patterning in a principled manner. Our work was motivated by accumulating evidence showing that oscillatory activity at resting state reflects the integrity of the underlying networks and its characterization can result to reliable biomarkers of various disorders (Stam et al., 2005, 2007; Babiloni et al., in press; Uhlhaas and Singer, 2006; Xie and He, 2012). In conjunction with recent findings about the coupling of ongoing regional brain activity with subsequent response (Makeig et al., 2002; Jansen et al., 2003; Laskaris et al., 2003; Fell et al., 2004; Mazaheri and Jensen, 2010; VanRullen et al., 2011), this opens the possibility that there is some extra information, inherent in the ensemble of single trials, that is overlooked during signal averaging. This information may come in the form of genuine response variability and might be recovered via appropriate signal manipulations. It was the scope of this work to built a descriptor of response variability that would emphasize the differences in AERPs between patients with amnestic mild cognitive impairment and healthy (NI (*Non Impaired*)) individuals and subserve a reliable MCI detection.

Toward this end, a well established methodological framework (Laskaris et al., 2004) for studying the single-trial response variability (within a subject's data) is extended so as to handle ST-data across populations and modified so as to comply with the discriminative aspects of MCI detection task. A rough sketch of our data analytic methodology is provided in Fig. 1, in which all the key ingredients are illustrated using real data (a subset of the overall dataset), while confining presentation within a 2D space. The first step, that is feature extraction/selection (presented in Section 3.1), is based on a gross comparison between the temporal patterning of response in MCI and NI subjects. In Fig. 1a, using the two group grand-averaged waveforms (derived by averaging all corresponding individual STs) two latencies have been selected and denoted as $t_{\mathbf{A}}$ and $t_{\mathbf{B}}$. The first one corresponds to the highest deviation associated with the N200 peak and the other with the P300 peak. The signal amplitudes at these latencies constitute the pair of features extracted from each ST-response. Considering that each ST-response in represented by a single dot colored according to its membership (red for MCI and blue for NI), the point-diagram of Fig. 1b reflects response variations with emphasis on inter-group differences. During the second step (described in Section 3.2) the whole spectrum of variation is summarized by segmenting STs into homogeneous groups, based on the extracted feature vectors, and deriving representatives. The estimated reference vectors (code vectors) are indicated with black circles in Fig. 1c and the overlaid *voronoi-diagram* delineates the local regions in feature space, known as *voronoi regions*, that are associated with them. The voronoi regions are ranked from the one dominated by STs of healthy subjects to the one dominated by MCI STs. This ranking is indicated in Fig. 1d, both implicitly using color/size and explicitly via labels. It also lends the ranks to the list of prototypical responses (which have been derived by averaging all the STs associated with a particular voronoi region) shown in Fig. 1e. In the final step, that is the vector quantization (VQ) of response dynamics (described in Section 3.3), the voronoi regions are treated as multidimensional bins. The successive feature vectors $\mathbf{x_i}(t_{\mathrm{lag}}) = [x_i(t_{\mathrm{A}} + t_{\mathrm{lag}})\ x_i(t_{\mathrm{B}} + t_{\mathrm{lag}})]$, that are 2D row-vectors extracted from the ith single-trial signal $x_i(t)$ and refer to a time-lag parameter, are forming a response trajectory. This trajectory can be represented as a distribution over the previously defined voronoi regions. The traces of two such single-trial responses from a particular MCI patient are depicted in Fig. 1f and g. By accumulating across trials, the distribution of ST-trajectories, we obtain a histogram per subject reflecting the response variations. Such a histogram can be thought of as a response profile with semantics defined not only by the relative number of counts, but also by (and mainly due) the ranked voronoi regions. Two such histograms (for a patient and a healthy subject) have been included in Fig. 1h.

Using single-trial data from a group of 25 amnestic MCI patients and an equally sized group of aged-matched subjects, we tested whether the introduced response representation, named hereafter *discriminative VQ-profile*, facilitates a more reliable classification than representations based on averaged responses.

2. Experimental data

2.1. Subjects

The MCI group consisted of a total of 25 amnestic MCI patients (mean ± SD: age = 69 ± 7). An additional elderly group of 25 healthy individuals was also formed spanning a similar range of ages. The subjects were recruited at the Day Center of Greek Association of Alzheimer Disease and Relative Disorders (GAADRD). The study was approved by the Ethics Committee of the Greek Association of Alzheimer Disease and Relative Disorders. The diagnoses of MCI were made according to published criteria. The "typical criteria," adopted at the GAADRD Day Centers, were adapted from the most recent criteria outlined in Petersen and Morris (2005). Individuals were classified as normal if no neuropsychological measure fell more than 1.5 SD below age-appropriate norms in any cognitive domain. Impairment required scores to fall more than 1.5 SD below age appropriate norms on only one test within a domain. Specifically, individuals were identified with MCI if objective memory performance fell more than 1.5 SD below their age appropriate norms on the WMS-R LM subtest. This was an entirely dichotomous designation, classifying individuals as either "normal" or "amnestic MCI," and mirrored the dominant method by which objective memory impairment was defined in the early MCI literature as well as in more recent large clinical studies.

Evaluations typically included one or more composite or global measures of cognitive function such as the *Mini-Mental Status Exam*