Protocols of data collection to support early diagnosis of Alzheimer’s disease

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Abstract

The aim of the paper is to introduce developed protocol of EEG data acquisition for early diagnosis of dementia of Alzheimer type. Proposed protocol developed for coordination and standardisation of data acquisition process in order to allow performance of multicentre research. This protocol based on two experiments which use an audio and visual stimulation of study participant. Collected data will be analysed for estimation of differences in information processed cortical functional structures at different stages of a neurodegenerative process.

Keywords
Study protocol, EEG, dementia, Alzheimer’s disease, diagnostics

1. Introduction

Alzheimer’s disease (AD) is the most common form of neurodegenerative disorder which is characterized by cognitive and intellectual deficits and behavioural disturbances. Nonetheless, the current clinical diagnosis of AD is imprecise. At present, AD diagnosis fall broadly into three categories - early and pre-symptomatic, probable AD and definitive AD. At the early and pre-symptomatic stages, the diagnostic accuracy of AD is often low when confusion with other dementias is common [5,9]. Using current consensus criteria, the accuracy for probable AD is approximately 90% and for definitive diagnosis of AD, autopsy confirmation is a mandatory requirement [7].

Several drugs and therapy can be administered to slow down the progression of the disease, nonetheless, they are most effective at symptom onset. Thus, early diagnosis of AD, is highly desirable before neurodegeneration becomes more severe and is a critical issue in dementia research.

The EEG is an attractive tool in clinical practices and is widely used in dementia research due to its non-invasiveness and real-time depiction of brain activities. This has prompted the development of a large number of EEG analysis algorithms ranging from classical spectral analysis to nonlinear dynamical analysis [10,11]. Nonetheless, the success of these algorithms depends not only on its inherent mechanisms, but also on the data they are analysing. Therefore, good recording protocols and experimental paradigms are crucial to ensure the quality of the data so that the analysis results would be meaningful. For EEG data collection in dementia research, the minimum level of information such as the age, gender, neuropsychological test scores, disease duration, etc. are required. Table I provides a summary of these information.

In this paper, we present our work on the development of a unified protocol for subject-specific serial EEG study. The main aim of this is to establish a multicentre research for early detection of
AD. A unified protocol has a lot of advantages. It will allow new data to be compatible across centres and therefore will widen potential of analysis and increase significance of results by enlarging sample size. We have focused on two functional EEG tests (visual and auditory) as the cortex plays an important role in their activities. The hypothesis is that neurodegenerative processes during AD will be reflected in dynamics of electrical potentials of the brain. These tests have already been used in the diagnosis of early stage AD, however we believed that their potentials have not been fully explored since by large, only classical techniques such as Fourier analysis have been applied to data obtained [3,4,6,9]. We believed that a good recording protocol coupled with advanced analysis techniques such as those from nonlinear measures would provide more insights into the data and thus revealing more about the patient’s condition(s) for more robust diagnosis.

The remaining of this paper is organised as follow. Section 2 discusses the study design, EEG recording including functional tests, and discussions on the appropriate type of data analysis methods. In Section 3, conclusions and future work are presented.

**Table 1.** Minimum level of information required for dementia research

| • Age of each subject - many EEG measures depend on age (even a small age difference between patients and controls could severely bias the results) |
| • Gender |
| • Education of subject (e.g. is subject a university graduate?) – education has an impact on results. |
| • Disease duration (in years); |
| • Type of disease (e.g. probable AD, vascular) and diagnosis criteria |
| • Disease severity (MMSE, CDR scores). |
| • MRI findings of each subject (if possible, to exclude other causes); |
| • Therapy and drugs administered (if any). |
| • Inclusion and exclusion criteria during subject recruitment. |
| • EEG recording details (e.g. electrode placement, recording conditions e.g. awake, experiments, sampling rate, length of recording, data pre-processing if any etc) |

2. Protocol of EEG data acquisition

2.1. Study design

*Number of patients.*

Target is 500 cases, but assuming drop out will complete studies on 600 study participants: 120 normal elderly subjects, 240 subjects with mild cognitive impairment, 240 subjects with probable Alzheimer dementia.

*Duration.*

The trial will be conducted in two phases over three years. Phase 1: the collection of data (24 months, data collection points: 0, 6, 12, 18, 24 months), and phase 2: the analysis of data (12-36 months).

*Inclusion/Exclusion criteria.*

All study participants will be between 55 and 90 years of age, have an informant able to provide an independent evaluation of functioning and will speak English. All subjects must be willing and able to undergo all testing procedures including MRI scan and agree to longitudinal follow-up. Specific psychoactive medications will be excluded. General inclusion/exclusion criteria are shown below:
1. Normal subjects: MMSE scores between 24 and 30, a CDR of 0, non-depressed, non-MCI and non-demented.

2. MCI subjects: a memory complaint, have objective memory loss measured by education adjusted scores, a CDR of 0.5, absence of significant levels of impairments in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia.

3. AD subjects: MMSE between 18 and 26, CDR of 0.5 or 1.0, and meet CAMDEX criteria for probable AD.

2.2. EEG recording

*Baseline EEG.*
In addition to routine EEG, an eyes-closed and eyes-opened EEG will be recorded for three minutes each from all participants at the beginning of the additional study session [2]. These records will be used for comparative analysis with data acquired from another experiments. The next two procedures will enable investigators to measure the ERP. These procedures will be accompanied breaks for rest and additional instructions for study participants.

*Functional EEG tests.*

*Photic driving responses.* EEG signals will be recorded during a state of relaxed wakefulness, during intermittent photic stimulation at frequencies of 5, 10, 15 Hz, and during relaxed wakefulness between stimulations [3,4,6,9]. The subjects will keep their eyes closed throughout the experiment. Each stimulation consisted of flashes presented at a fixed frequency for 50-60 s, with the same periods between stimulation runs. The photostimulator should have a lamp with flashes of approximately white light having duration of less than 20 µs. The lamp will be positioned at a distance of 25 cm from the eyes, with dim surrounding light.

*Auditory event-related responses.* The ERPs will be obtained using an auditory oddball paradigm [9,1,8]. Binaural audiometric thresholds will determine for each subject using a 1000Hz tone. The evoked response stimulus will be presented to both ears using stereo speakers at amplitude comfortable for their hearing level. The stimulus consist of tone bursts 100ms in duration, including 5ms inset and offset envelopes. Tones of 1000Hz and 2000Hz will be presented in a random sequence with the tones occurring in 65% and 20% of the trials respectively. The remaining 15% of the trials should consist of novel sounds presented randomly. These included 60 unique environmental sounds that will edited to 200ms duration. A total of 1000 stimuli, including frequent 1000Hz (650 stimuli), infrequent 2000Hz tones (200 stimuli) and novel sounds (150 stimuli) will delivered to each subject with an interstimulus interval of 1.0-1.3 seconds. The subjects will be instructed to press a button each time they heard the 2000Hz tone. With frequent breaks (e.g. approximately three minutes of rest every five minutes), the data collection process will last about 30 minutes per subject with each session proceeded by a 1 minute practice session without the novel sounds.

2.3. Discussion

*Types of suitable analysis methods.*
In order to ensure that the results obtained from the analysis are meaningful, we discuss in this section several analysis techniques which we deemed suitable for the data obtained through the proposed experimental paradigm.
In the proposed research, we are going to investigate:

- Source localisation of harmonically induced oscillation during photic stimulation.
- Differences between fundamental and harmonic responses for different stimulation frequency.
- Harmonic responses attenuation in rest period.
- Source localisation of different ERP components (not only P300).
- Differences between target and novelty ERP components dynamics.

The types of analysis techniques which we envisage suitable for the data include ICA, source localisation and nonlinear measures.

- ICA as relatively recently introduced method of blind source separation exploits the idea that EEG is mixture of independent signals. This method will be useful for study of correspondence of harmonic oscillations of EEG in driving response conditions.
- Source localisation can estimate the cortical diffusion of ERP components. In order to improve a time resolution of localisation we going to use wavelet transformation of EEG. We assume that patterns of diffusion of ERP components will be significantly different in different stages of disease.

Following approaches based on theory of dynamics of nonlinear systems could provide insights into the underlying systems producing the EEG oscillations.

- Synchronization likelihood is measurement of interactions between cortical areas which should reflect degree of neurodegenerative processes.
- FD, D2 and L1 can be used to study the dynamics of the EEG in the conditions of functional loads.

3. Conclusion and future work

In this paper, we have reported our work on a unified protocol for subject-specific serial EEG study. The main aim of this is to establish a multicentre research for early detection of AD using high quality data obtained through appropriate experimental paradigm. We have presented the study design, EEG recording (baseline and functional EEG) paradigms and provided a short discussion on the type of analysis techniques which is suitable for the data obtained. Clearly, albeit the advantages and potential offered by electrophysiological markers in the early detection of AD, it is important to include other markers such as those from genomics, biochemical, neuroimaging modalities for a more comprehensive and sound diagnosis. These will be included in the extension to the current protocol.
4. References