Event-related Potentials and the Diagnosis of Alzheimer's Disease—The COGNISION™ System

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Abstract

Alzheimer's disease is a major cause of cognitive decline among older people. Current diagnostic approaches rely primarily on cognitive symptoms. Recently proposed changes in the definition of the disease place more emphasis on the use of biomarkers (such as neuroimaging or cerebrospinal fluid markers) in the hope of allowing earlier and more definitive diagnosis for research and, eventually, clinical purposes. Event-related potentials (ERP) represent another promising biomarker approach. Alzheimer's disease has been demonstrated to have a recognizable ERP signature. Recent advances in ERP technology may make the process painless, non-invasive and portable. These advantages suggest that ERP should be further considered as a potential biomarker for Alzheimer's disease.

Keywords

Alzheimer's, event-related potentials (ERP), bio-marker, COGNISION™

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Alzheimer's disease (AD) is a major source of disability and mortality among older people. AD prevalence is rapidly increasing with increasing lifespan and a larger absolute number of elders. Current treatments, such as cholinesterase inhibitors or N-methyl-D-aspartic acid antagonists are supportive or palliative in nature, and are based on optimizing neurotransmission, but do not alter the underlying disease process. Their effects are modest and not every patient responds positively.

In recent years enormous efforts have been under way to improve understanding of the disease and develop improved treatments. This article examines new developments in the definition of the disease and the growing importance of biomarkers in diagnosis. It will focus on the possible use of event-related potentials (ERP), an electrophysiological parameter, as a cognitive AD biomarker.

Clinical Diagnosis of Alzheimer's Disease

Clinical diagnostic criteria of AD rely primarily on cognitive parameters and are based on excluding other possible causes of cognitive deficit. Such parameters include:

- progressive, disabling loss of memory (especially episodic memory);
- loss of other cognitive skills, such as language and executive function; and
- diminishing functional ability, such as the ability to carry out activities of daily living.

In clinical practice, laboratory testing and neuroimaging serve primarily to help rule out other potential conditions. One must have substantial loss of cognition to qualify for the diagnosis of AD.[1]

Pathological Characterization of Alzheimer's Disease

AD is characterized pathologically by amyloid plaques and neurofibrillary tangles, which are comprised primarily of misfolded proteins, along with atrophy. Amyloid is widely believed to be central to the pathogenesis of AD, a point of view known as the 'amyloid hypothesis'. Plaques are believed to evolve through a complex pathway, commencing years before clinical memory symptoms of AD. Plaques and tangles cannot be visualized or detected by standard clinical imaging or laboratory techniques.[2] However, amyloid plaques can be visualized with advanced positron emission tomography (PET) imaging systems utilizing labeling compounds that can currently only be used in specialized research settings (although new approaches are under development).[3,4]

The recent failure of several amyloid-based clinical therapeutic trials has provoked a rethinking of treatment strategies in AD. Some

researchers have become skeptical of the amyloid hypothesis.[5] Many others believe that memory symptoms are a relatively late development in AD and that a successful therapy, including an amyloid-based strategy, depends on intervening earlier in the disease process.

A New Definition of the Disease

In order to facilitate this strategy, a new and evolving definition of AD has been created that relies on biomarkers along with progressive cognitive decline. This approach defines AD more clearly as a brain disease of plaques and tangles, rather than strictly being a cognitive disorder or dementia. The three proposed categories include:

- Alzheimer's disease dementia;
- mild cognitive impairment due to Alzheimer's disease; and
- pre-clinical Alzheimer's disease.

This definition greatly expands the number of individuals counted as having the disease by including a large group of asymptomatic people. It is hoped that redefining AD in this way will facilitate a unified research program and prompt a search for earlier interventions. Under the old definition of AD that relies on clinical diagonsis, new drug development aimed at intervention at the earliest possible stage would be greatly hampered as the industry is reluctant to expend enormous resources on a condition that is not recognized as a disease.[6]

Developing Biomarkers

The new strategy depends on refining or developing a set of biomarkers that can reliably diagnose the condition as early in the process as possible. Current candidate marker approaches include:

- structural or functional magnetic resonance imaging;[7]
- cerebrospinal fluid protein analysis;[8,9]
- blood or genetic markers using apolipoprotein E4 and other proteins;[10] and
- PET scanning.

All of these approaches have advantages and disadvantages and may ultimately be suitable for various purposes or stages of disease. It is highly likely that combinations of biochemical and cognitive biomarkers may be necessary to achieve the desired level of diagnostic accuracy.

There are many challenges to implementing this new paradigm. The process of developing biomarkers is incomplete and ongoing. The expense and intrusiveness of obtaining certain markers limits their usefulness (e.g. lumbar puncture for cerebrospinal fluid or the lack of portability of diagnostic devices, such as advanced PET systems with radio-labeling compounds).

Expanded use of biomarkers will be much easier to implement as a research tool than in clinical practice. The cost and difficulty of screening large numbers of asymptomatic individuals for clinical purposes with lumbar puncture or PET are obvious.

Therefore, for the immediate future memory symptoms are likely to continue to be the trigger for clinical assessment. Physicians will need better diagnostic tools to clarify diagnosis in clinical practice, hopefully including some type of biomarker.

The use of Electroencephalography-based Technology

The limitations of previously discussed AD biomarkers, in terms of evaluating cognitive deficit, leave room for additional approaches. One such approach is ERP. This is an electroencephalography (EEG)-based technology that can also serve as an AD biomarker. ERP is less expensive, intrusive and more portable than most currently proposed biomarkers, so it holds promise.

Event-related Potentials in the Brain

ERPs are a subset of EEG signals of cortical activity. ERP is a specialized form of EEG and may be thought of as a subset of evoked potentials. Evoked potentials are familiar to many neuroscientists as EEG waveforms provoked by sensory stimuli, often auditory or visual. Such evoked potentials are useful in various situations, such as brain mapping or in the diagnosis of certain types of deafness or blindness. The evoked potentials represent the brain's reception and registration of the sensory input. However, ERPs occur later. They represent the brain's higher cortical analysis of the initial signals. This is the essence of ERP utility in disorders such as AD. ERP is a cognitive biomarker representing actual changes and slowing in cognitive processing, as opposed to detecting the presence of an abnormal protein (a marker that may not have a causal link to cognitive changes). Compared with structural or physiological markers, ERP is an absolute rather than a relative marker, in that a single determination has meaning; scans may require multiple determinations over time for comparative purposes.[11,12] Certain ERP signals are believed to represent higher cognitive analysis or processing, rather than simple registration of an external signal (such as a tone or flashing light). Signals must usually be averaged over a number of repetitions of the same event to 'average out' background EEG 'noise'.

Event-related Potentials as Cognitive Biomarkers of Alzheimer's Disease

The 'Odd-ball Paradigm'

An ERP 'odd-ball paradigm' is routinely employed to assess novelty detection and memory storage of patients. The paradigm entails giving two different stimuli in random order, with one occurring less frequently. The subject is then asked to discriminate between the less frequent (target) and the more frequent (standard) stimuli. In this situation, the target stimulus elicits an ERP response (such as the P300), whereas the standard stimulus does not. The ERP signal reflects the higher cognitive processes required to make this discrimination. Despite having determined this, the exact mechanism of ERP signals is not known.[11]

Several published studies examine ERP and AD. Recent studies include one by Polich and Corey-Bloom, in which 16 early-stage AD patients were compared with normal elderly controls using ERP P300, with four different auditory and visual odd-ball tasks. P300 amplitude was lower and peak latency longer in the AD group, especially in relatively easier tasks. The authors concluded that P300 is sensitive to early brain changes in AD and that easier-to-perform stimulus discrimination tasks were the most useful.[11]

A relatively well-known feature of the ERP wave is the P300 peak. In ERP terminology, P represents a positive valence of the EEG waveform, occurring about 300ms after the external stimulus. In fact, P300 amplitude and latency have been demonstrated to change systematically with a variety of neurological conditons, including AD.[11] Unfortunately, P300 alone is not a sufficiently accurate marker of AD, as there is too much individual variation.

Advances in Event-related Potential Technology

ERP technology has advanced greatly in recent years. Some modern ERP systems feature a wearable electrode cap, precluding the necessity of individual EEG electrodes with gel or scalp abrasion. Some ERP studies have demonstrated the importace of combining ERP responses to different stimuli and collected from different cortical areas to achieve higher diagnostic accuracy. Some of these systems use advanced pattern-recognition software to automatically evaluate ERP test data. These developments greatly enhance the applicability of ERP in a physician's office.

Polikar et al. reported on an ERP study where signals from several EEG electrodes were recorded and features in addition to the P300 were automatically combined using artificial neural networks decision fusion algorithms to achieve very high diagnostic accuracy between Alzheimer's patients and healthy, age-matched controls. In their approach, multiple features from several electrodes were merged using a special algorithm developed specifically for this purpose. They reported that this method could equal the diagnostic accuracy of many highly trained clinical specialists and could exceed the diagnostic accuracy of most community physicians.[13] A sufficient database now exists to allow for discrimination of AD *versus* normal controls early in the course of illness.[14]

The COGNISION™ System

Neuronetrix has developed a new system utilizing an approach of this type. The COGNISION™ system is a handheld, wireless device that can be used in an office environment. It includes an ergonomic headset with high-performance active electrodes and integrated earphones. The system performs a selection of standardized auditory ERP tests that have been developed to target specific cognitive domains. Various classification studies may be automatically performed using advanced neural network pattern-recognition methods. The test data and classification results are stored in an online electronic patient record system. This record system may be useful in office-based diagnosis, as well as in research and drug development. Changes in the ERP signal over time in AD may allow clinicians to monitor progression of the disease or follow response to therapies.

The COGNISION system is currently undergoing clinical trials. The portability, non-invasiveness, and inexpensive nature of the test make it a promising tool in a general physician's office.

Conclusion

A new and evolving definition of AD has been created that relies on biomarkers along with progressive cognitive decline, which will hopefully aid earlier diagnosis and treatment of the disease. It is hoped that the increased number of patients diagnosed with AD will facilitate a unified research program expanding the knowledge and application of biomarkers and eventual treatment options for AD.

AD has been demonstrated to have a recognizable ERP signature, which makes ERPs good AD biomarker candidates. Recent advances in ERP technology may make the process of measuring such a biomarker painless, non-invasive and portable. These advantages suggest that ERP should be further considered as a potential AD biomarker. ■

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