

BrainView - FREQUENTLY ASKED QUESTIONS

Cognitive disorders such as age-related dementias are notoriously difficult to diagnose accurately, especially in the early stages. Even at NIH-sponsored Alzheimer's Disease Centers, diagnostic sensitivity ranges from 70.9% to 87.3%, while specificity is only 44.3% to 70.8%[1]. This clearly demonstrates the need for more reliable tools to help with these complex diagnoses. Standard neuropsychological tests may be useful to elucidate specifically impaired cognitive domains; however, they do not provide physiological measures related to the underlying etiology. Modern electrophysiological techniques such as Quantitative EEG (QEEG) and Event-Related Potentials (ERP) are becoming the forefront in neurodiagnostic testing and provide physiological evidence of disease in the absence of clear psychometric results.

What is involved in a BrainView® testing session and how are the results presented to the clinician?

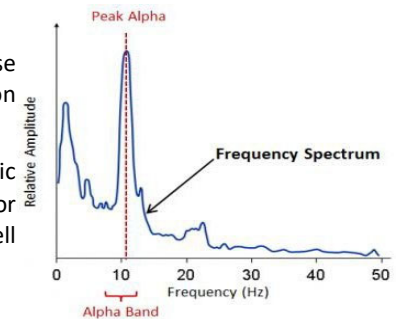
During a standard 20-minute testing session, EEG and ERP tests are performed. At the end of the session, a Patient Report is automatically generated that contains an audiogram, results from the QEEG/ERP tests, and an editable field for the treating physician to record the clinical findings.

What tests does BrainView® perform and how do the results reflect cognitive processes?

EEG

Resting EEG is a recording of the ongoing spontaneous electrical activity in the brain. Because neurodegenerative disorders adversely impact functionally connected neural networks, their effects on cognition are reflected in EEG measures [5].

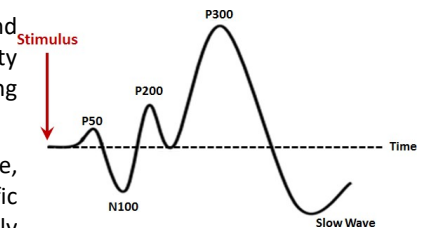
An analysis of the spectral features of the EEG (often called quantitative EEG or QEEG) can provide specific biomarkers of cognitive performance. One useful biomarker is the dominant frequency in the α band, or Peak Alpha Frequency (PAF). PAF reflects cognitive and memory performance in particular [6], and is well suited as a reliable biomarker of neurodegeneration in diseases such as Alzheimer's disease (AD).



ERP

An ERP (also called auditory evoked potentials) is part of the EEG which is generated by sensory and cognitive processing of a sequence of external stimuli. ERPs reflect the summed synaptic activity produced when a large number of similarly oriented neurons fire in synchrony while processing information related to the stimulus stream [7].

The stimuli in the ERP test are grouped into sequences of repeating sounds or visual cues. The type, timing, and sequence of stimuli (often called an "ERP paradigm") are organized to target specific cognitive processes such as selective attention, memory encoding, etc. While the brain subconsciously analyzes the incoming stimuli, EEG time-locked to each stimulus is recorded. At the end of the test, the time-locked EEG "epochs" are averaged according to stimulus type, and all brain activity not related to the specific stimulus group is filtered out. What is left are ERP waves that represent the physiological responses related to the cognitive processes evoked by each stimulus type played during the test.



These ERP waves contain a sequence of positive and negative peaks, or features, that have been extensively characterized in the scientific literature. The early peaks are primarily "sensory" responses that depend largely on the physical parameters of the stimulus. The sensory features are followed by later "cognitive" peaks which reflect information processing, and can be used to detect and quantify cognitive deficits associated with AD and other dementias [8].

What does the patient experience during a BrainView® testing session?

A BrainView® testing session optionally includes a practice ERP test, a full ERP test, and a resting-state EEG test. The practice ERP test is designed to familiarize the patient with the behavioral task associated with the test. The full ERP test involves a standard visual and auditory oddball (or P300) paradigm which has been used in clinical and scientific research for decades [10] and has shown sensitivity to the sensory and cognitive deficits associated with AD [11]. During this part of the testing session, visual and auditory stimuli (a combination of three different tones) are presented to the patient through earphones and the patient is instructed to press a button when they hear the high pitch stimulus. Before the ERP test is complete, the patient is asked to relax while resting EEG is being recorded. At the end of the EEG, the BrainView® System will notify the test administrator that the testing session is complete. The whole testing session can be completed in about 20 minutes.

What results are generated from a BrainView® testing session?

Data collected from the of the ERP test and subsequent analysis:

Results from the ERP test include amplitude, latency, and average amplitude for the ERP features extracted from the ERP wave. Accuracy, false alarms, and reaction time for the target detection task associated with the test are also measured.

ERP peak “amplitude” is calculated as the difference between mean pre-stimulus baseline “0” and maximum peak amplitude. “Latency” is defined as the time point following stimulus presentation corresponding to the maximum amplitude (peak) for the specific feature [12], [13]. Finally, ERP “average amplitude” is defined as the averaged voltage over the time window specified for each feature [7]. Average amplitude is highly correlated with amplitude for the same ERP features, and likely shares the same functional interpretation [14]. Thus, it can be used as a proxy measure to confirm amplitude data, or in situations where an ERP peak might be difficult to identify.

For the target detection task, “accuracy” is calculated as the percent of correct responses to target tones, while “false alarms” indicate button presses to non-targets. “Reaction time” is calculated as mean time from stimulus onset to button press [15].

P50

The P50 is an early cortical potential that is elicited in response to both standard and deviant stimuli. Its amplitude in response to standard stimuli is increased in subjects at heightened risk of developing AD [16], [17]. The increase in P50 amplitude is no longer significant in subjects with probable mild AD. However, these subjects still show an increase in the peak average amplitude [18]. The P50 is thought to reflect neural activity in the temporal gyrus, a region that is important for speech and language. Thus, an increase in P50 amplitude might reflect abnormal language function. Indeed, subjects with MCI have shown altered long-latency brain potentials associated with semantic processing [19].

N100

The N100 is a large, negative-going evoked potential that follows the P50. Its amplitude shows a large decrease in subjects with mild AD. The N100 reflects bottom-up information such as stimulus characteristics [18], [20]. However, this ERP feature is modulated by attention and memory related variables [21], [22]. Thus, the lower amplitude of the N100 in subjects with mild AD is consistent with attention and memory deficits in these subjects. Indeed, neuropathological studies show that sensory cortices are typically spared until the advanced stages of AD [23]. A decrease in N100 amplitude could reflect changes in regulatory inputs from brain regions that are involved in higher cognitive processes and are more directly affected by the disease in its early stages. For example, the prefrontal cortex and the nucleus basalis have been shown to modulate auditory cortical responses to sound [24], [25].

P200

The P200 is a positive deflection in the ERP wave that peaks at about 200ms after stimulus onset. Its functional interpretations include attention modulation of non-targets stimuli and stimulus classification [26]. It has been suggested that individuals with reduced P200 amplitude have a weaker representation of auditory signals, and that might contribute to slower reaction times to the stimuli and reduced accuracy in stimulus classification [27]. Consistent with this hypothesis, subjects with mild AD have lower P200 amplitude than healthy individuals in response to the standard stimulus of the oddball paradigm and show lower accuracy and longer reaction time in the target detection task associated with the test.

N200

The N200 is a negative peak that in the ERP wave for the target stimulus immediately precedes the P3b. This ERP feature is linked to the cognitive processes of stimulus identification and distinction [28], and its peak latency has been shown to correlate with measures of executive function and attention [29]. Published studies have reported delayed latency [29] and smaller amplitude [30] for the N200 in AD subjects. Indeed, N200 latency has proven useful in separating AD subjects from subjects with mild cognitive impairment (MCI) and healthy controls (HC) [29], while N200 amplitude has been used in combination with P300 latency to track longitudinal changes in overall cognitive function in MCI [30].

P3a

In active two-deviant oddball paradigms, the P3a is generated in response to the distractor stimulus. This ERP feature has been associated with engagement of attention and processing of novel information [31]. The peak amplitude is a measure of focal attention, and has been shown to positively correlate with executive function [32]. The P3a latency reflects orientation to a non-target deviant stimulus [33]. Consistent with reports of decreased attention and executive function in neuropsychological testing in subjects with mild AD [34], P3a amplitude is significantly reduced in this population. Moreover, the large group differences in P3a amplitude together with reports of a decline in attention and some executive skills very early in the disease [35], [36] suggest that this ERP feature could be a useful measure of cognitive deficit since the preclinical stage of AD.

P3b

This ERP feature is elicited when a deviant stimulus is associated with a task, and reflects an update in working memory [31]. P3b amplitude is determined by the amount of attentional resources allocated when working memory is updated [37]. P3b latency reflects stimulus evaluation and classification speed [38], [39]. The majority of studies that have looked at differences in P3b between AD subjects and HC

have found that P3b amplitude was typically smaller, and P3b latency was longer in subjects with AD [11]. Moreover, when subjects were administered an auditory oddball paradigm similar to the one used for BrainView® testing, group differences were larger for P3b amplitude than latency [11].

Slow Wave

The Slow Wave is a negative deflection that follows the P3b. This ERP feature has frontal and central scalp distribution [15], and reflects a final stage of stimulus evaluation [40]. Slow Wave amplitude correlates with task demands and it is inversely correlated to stimulus detection accuracy, suggesting that an increase in peak amplitude might reflect the need for further stimulus processing. Slow Wave latency is affected by task difficulty, and the relative ease of categorizing events in an oddball test probably accounts for the early onset and short duration of the Slow Wave in this ERP paradigm [40]. Slow Wave latency has been recently shown to be delayed in subjects with mild AD [14]. These data are consistent with a previous report of increased Slow Wave latency in MCI [30], and suggests that AD subjects might require more time for stimulus processing than HC.

Target Detection Task

In addition to changes in the ERP wave, subjects with mild AD show decreased performance in the behavioral task associated with the ERP test. This group of subjects has lower button press accuracy and longer reaction time. Work by Polich and Corey-Bloom has shown increased response time and error rate in AD patients across different auditory and visual oddball paradigms [11]. Recent data confirm these findings when patients were tested in outpatient settings, and suggest that results from the behavioral task of the ERP test could help discriminate subjects with mild AD from healthy aging [14].

Data collected from the EEG test and subsequent analysis:

Peak Alpha Frequency

Peak alpha frequency (PAF) is defined as the discrete frequency with the highest magnitude within the alpha range and is measured in Hz. PAF decreases with increasing age [41], and has been shown to reflect performance in various cognitive functions, including attention, arousal, working memory, long term memory and reading [41]. In general, a decrease in PAF frequency indicates deterioration in cognitive performance. Indeed, subjects with mild-to-moderate AD have significantly lower PAF than matched controls [42].

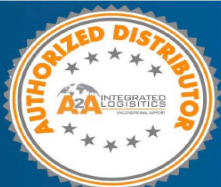


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How does BrainView® benefit patients and impact delivery and cost of care?

- Data from EEG and ERP tests can provide sensitive and reliable physiological measures of cognitive deficits. Indeed, the P3b feature of the ERP test was proposed as a useful assessment tool for cognitive deficits associated with AD in the original NINCDS-ADRDA criteria for clinical diagnosis of AD [43]. QEEG and ERP testing are also recommended for AD diagnosis in a report from the AAN and ACNS published in Neurology [44]. Additional support for “*biomarkers showing that nerve cells in the brain are injured or actually degenerating*” was recently included in the FAQ section of the new criteria and guidelines for AD diagnosis published in 2011 [45]. Though some of the changes in ERP and EEG measures are not specific to a single disease, others can help identify the pathophysiological etiology of a patient’s dementia. For example, ERP can help differentiate dementia of the AD type from similar clinical symptoms due to depressive syndromes, as patients with AD show an increased latency for the P3b that is not present in subjects with depression [43], [46]–[48]. Moreover, the anterior-to-posterior scalp amplitude gradient for the P3b is reversed in patients with early dementia with Lewy Bodies (DLB), thus potentially helping discriminate DLB from AD [49]. Indeed, the use of ERP and EEG provides sensitive and relatively inexpensive measures of cognitive performance that can potentially decrease the need for more expensive and/or invasive testing, leading to more timely treatment and improved outcomes.
- ERP tests can be used for early detection of cognitive impairment and can facilitate early diagnosis of AD, thus helping patients and clinician optimize medical management and possibly reduce health care costs by delaying placement in a nursing home [50]. ERPs have been found to be altered in AD since the very early stages of the disease. Young pre-symptomatic individuals who carry mutations in the presenilin-1 and amyloid precursor protein genes show significant changes in ERP patterns years before the onset of behavioral symptoms and the development of AD [15], [51]. Moreover, ERPs have shown potential utility as biomarkers of disease progression and subsequent conversion to dementia in individuals with mild cognitive impairment (MCI). ERP responses to auditory stimuli contain discriminative information that predicts which MCI patients are likely to progress to AD [29], [52].
- Studies that looked at the ability of QEEG and ERP to discriminate subjects with mild AD from healthy aging show that these measures provide very high negative predictive value for AD, and could reduce the number of patients who might otherwise be referred for more extensive neuropsychological evaluations [53].
- Abnormal test results provide a positive, physiologic indication of impairment of cognitive processing and may be useful in identifying patients who show positive in FDG-PET and/or Amyloid PET scans [54]. Thus, ERP/QEEG testing could reduce the number of patients who would otherwise be referred for PET imaging.
- ERP and QEEG tests provide sensitive longitudinal measures to track decline in dementia patients. Indeed, ERPs have shown potential utility as biomarkers of disease progression and subsequent conversion to dementia in individuals with MCI [52], [55]. Moreover, ERPs have shown to reliably track increasing cognitive decline in patients with AD [30], [56]. These changes in ERP measures are also accompanied by a slowing of peak alpha frequency as the disease progresses [42], [57].
- ERP and QEEG tests can provide sensitive measures of the effects of cognitive enhancers currently used for the treatment of AD. ERPs provide a reliable assessment of the cognitive response to cholinesterase inhibitors such as donepezil, while the effects of the selective NMDA antagonist memantine on ERP features correlate with changes in MMSE score [58]–[60]. In addition, long term treatment with donepezil decreases deterioration of EEG measures over time [61]. Thus, ERP and QEEG can be useful for drug selection and/or to provide feedback to the patient regarding the importance of maintaining treatment.



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