COGNISION

CLINICIAN FREQUENTLY ASKED QUESTIONS

Overview

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 COGNISION® testing session and how are the results presented to the clinician?

During a standard 60-minute testing session, pure-tone audiometry and both 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 COGNISION® perform and how do the results reflect cognitive processes?

Audiometry

Hearing loss (HL) can confound the clinical investigation of cognitive impairment when performing auditory ERP and/or standard psychometric testing. Furthermore *"mild to moderate hearing loss can be more devastating for those with AD than for aging individuals with normal cognition"*[2]. Hearing loss may even play a role in the cognitive decline in early Alzheimer's patients.

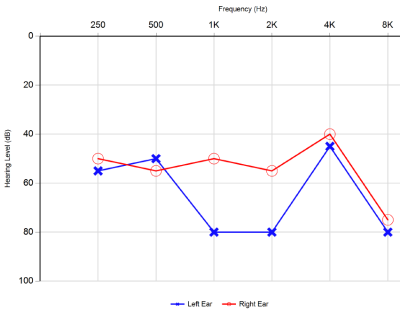

Figure 1: Audiogram

Studies have shown a *"robust relationship of even early memory loss and tests of central auditory function"*[3]. In fact, *"Anytime you have a patient who is at risk for dementia, any cognitive deficit, or traumatic brain injury, or any patient who has a hearing loss and problems with communicating that exceed what you would expect from that hearing loss, you have to think about auditory processing deficits."*[4].

An audiogram from the pure-tone audiometry test provides an objective measure of hearing loss at different frequencies (Figure 1). Thus, it is important to perform audiometric testing whenever performing cognitive evaluations in elderly patients.

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) (Figure 2). 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).

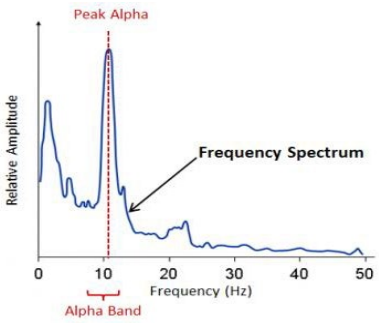

Figure 2: Peak Alpha from EEG data

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 <u>not</u> 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 (Figure 3).

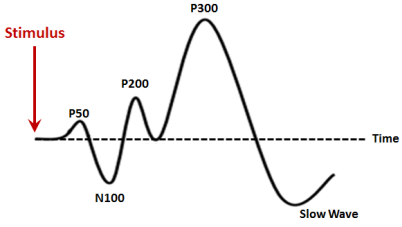

Figure 3: Example of an ERP wave

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 COGNISION® testing session?

A COGNISION® testing session optionally includes an ANSI S3-1996[9] compliant pure-tone audiometry test, a practice ERP test, a full ERP test, and a resting-state EEG test. During the audiometry test, the patient is instructed to press buttons on the COGNISION® controller whenever they hear any one of 5 pure-tone beeps played at different volume levels. 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 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, 400 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. After the ERP test is complete, the patient is asked to relax while resting EEG is being recorded. At the end of the EEG, the COGNISION® System will notify the test administrator that the testing session is complete. The whole testing session can be completed in about 60 minutes.

What results are generated from a COGNISION® testing session?

Data collected from the Audiometry test:

Audiogram

The output from the audiometry test is an audiogram showing hearing threshold levels (HTL) in dB for the left and right ears for 5 pure-tone frequencies from 250-8000Hz. HTL of 0-25dB is within normal limits for older adults. 26-40dB HTL reflects mild hearing loss and may cause inattention, difficulty suppressing background noise, and increased listening efforts. Patients with this degree of loss may not hear soft speech. 41-55dB HTL is moderate hearing loss and these patients will have trouble hearing some conversational speech. Above 55dB HTL, patients have moderate to severe hearing loss which may make it difficult for them to perform an auditory ERP test. COGNISION® can compensate for up to 45dB HTL.

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 COGNISION® 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].

How can the data presented in the COGNISION® Patient Report be used to evaluate patients suspected of having Alzheimer's disease or other Alzheimer's-like dementias?

The following table provides reference values for 60-90-year-old cognitively health individuals and subjects with mild AD. The table is intended to help the physician quickly determine when one or more of the COGNISION® measures are within the generally accepted normal range, or may be abnormal and more consistent with early AD. All reference values other than PAF are from a recently published large multi-center clinical study [14]. PAF data are from Raicher, et al. [42].

TASK PERFORMANCE

Feature	Cohort	Value	**Interpretation** (see more detailed discussions above)
Button Press Accuracy (%)	Normal	94.1 ± 1.1	Decreased in subjects with mild AD. Reflects subjects' ability to pay attention to the test stimuli and is directly correlated with P3a amplitude, which is a measure of focal attention and executive function.
	Mild AD	82.2 ± 2.3	
False Alarms	Normal	1.1 ± 0.2	Increased in subjects with mild AD. May reflect prefrontal pathology that results in observable deficits in behavioral inhibition.
	Mild AD	4.9 ± 1.1	
Reaction Time	Normal	458 ± 11.4	Increased in subjects with mild AD. Prolonged reaction time may reflect slower stimulus processing and delayed executive function.
	Mild AD	499 ± 12.6	

ERP FEATURES

Stim	Feature	Cohort	Ampl.	Latency	Avg. Ampl.	**Interpretation** (see more detailed discussions above)
Standard	**P50**	Normal	2.77 ± 0.08	44.8 ± 0.4	0.29 ± 0.06	Increased amplitude in subjects at heightened risk of developing AD. May reflect activity in the temporal gyrus, a region that is important for speech and language. Increased amplitude suggests abnormal language function.
		Mild AD	2.95 ± 0.08	44.3 ± 0.4	0.60 ± 0.06	
	N100	Normal	-7.23 ± 0.14	93.0 ± 0.4	-4.56 ± 0.11	Decreased amplitude in subjects with mild AD. Reflects bottom-up information such as stimulus characteristics. Modulated by attention and memory related variables. Lower amplitude could indicate attention and memory deficits.
		Mild AD	-6.00 ± 0.14	95.2 ± 0.5	-3.73 ± 0.11	
	P200	Normal	5.26 ± 0.14	214.5 ± 1.0	3.44 ± 0.11	Decreased amplitude in subjects with mild AD. Reflects attention modulation and stimulus classification. Reduced amplitude may reflect a weaker representation of auditory signals and contributes to slower reaction times and reduced accuracy in stimulus classification.
		Mild AD	4.64 ± 0.12	211.7 ± 0.8	3.14 ± 0.10	
Target	**N200**	Normal	-0.31 ± 0.17	251.1 ± 1.3	2.84 ± 0.14	Delayed latency and smaller amplitude in subjects with AD. Linked to stimulus identification and distinction. Correlates with measures of executive function and attention. Amplitude has been used in combination with P3b latency to track longitudinal changes in overall cognitive function in MCI.
		Mild AD	-1.10 ± 0.16	257.9 ± 1.5	1.93 ± 0.13	
	P3b	Normal	6.03 ± 0.20	396.0 ± 2.8	1.92 ± 0.16	Delayed latency and smaller amplitude in subjects with AD. Amplitude is determined by the amount of attentional resources allocated when working memory is updated. Peak latency reflects stimulus evaluation and classification speed.
		Mild AD	4.42 ± 0.20	419.6 ± 3.3	1.40 ± 0.13	
	Slow Wave	Normal	-2.54 ± 0.20	563.6 ± 2.5	-0.02 ± 0.15	Delayed latency in subjects with mild AD. Peak amplitude correlates with task demands, is inversely correlated to stimulus detection accuracy and reflects the need for further stimulus processing. Latency is prolonged in subjects that might require more time for stimulus processing.
		Mild AD	-2.65 ± 0.18	575.4 ± 3.2	0.19 ± 0.15	
Distractor	**P3a**	Normal	5.88 ± 0.19	417.3 ± 2.4	3.40 ± 0.15	Decreased amplitude in subjects with mild AD. Associated with engagement of attention and processing of novel information. Amplitude is a measure of focal attention and correlates with executive function. Latency reflects orientation to a non-target deviant stimulus.
		Mild AD	3.63 ± 0.20	419.8 ± 3.0	1.26 ± 0.13	

EEG FEATURES

Feature	Cohort	Hz	**Interpretation** (see more detailed discussions above)
Peak Alpha Frequency	Normal	9.39 ± 0.12	Decreased in subjects with AD. Reflects performance in various cognitive functions, including attention, arousal, working memory, long term memory and reading. In general, a decrease in PAF frequency indicates deterioration of cognitive performance.
	Mild AD	8.34 ± 0.22	
		Not statistically different. Outside this range is abnormal for the population but may not be consistent with AD.	
		Consistent with Mild AD. Outside the Mild AD range may reflect later stage disease.	

How are COGNISION® test results recorded in a patient's records?

Upon completion of the COGNISION® test, clinicians can generate a Patient Report from within the COGNISION® software. This will create a formatted PDF file containing the test details necessary to properly document the procedure. After reviewing the test results, clinicians can update the Patient Report with their Study Findings.

The patient report can be generated and study findings documented by following a few simple steps:

1. "Create" the Patient Report from within the Test Admin or Patient Manager modules.
2. Compare the patient's "Task Performance", "ERP Features" and "EEG Features" test results with the data provided in the table above for cognitively healthy individuals and subjects with mild AD.
3. Note any abnormal values.
4. See the Interpretation section in the table and the ERP and EEG features sections above for interpretation of abnormal data.
5. Note the clinical findings in the "Study Findings" sections in the Test Admin or Patient Manger modules.
6. "Update" the Patient Report to include the clinical findings and save the PDF file to your patient record system.
7. Patient Reports are automatically saved in the COGNISION® System and can be accessed from the Patient Manager module. The Study Findings section can be edited and the report updated at any time.

For additional instructions on how to generate a Patient Report, please refer to the COGNISION® Help System.

How does COGNISION® 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.

Which codes are available to bill for COGNISION® tests?

The COGNISION® testing and evaluation session consists of three distinct procedures:

1) **Pure tone audiometry** (CPT 92552) to assess hearing deficits which are often comorbid with dementia and can confound the clinical workup.
2) **EEG 20-40 minutes** (CPT 95816) which includes both resting-state EEG test and a P300 ERP test (also called "auditory evoked potential").
3) **EEG digital analysis** (CPT 95957) to help identify important features from the EEG/ERP test data useful in evaluating cognitive function.

If a longer resting-state EEG test is clinically indicated and extends beyond 20 minutes, for example to allow for both eyes-open and eyes-closed testing, the EEG procedure listed above can be split into separate procedures using 2 distinct codes; CPT 95816 (EEG 20-40 minutes) and CPT 92585 (Auditory evoked potentials for evoked response audiometry and/or testing of the central nervous system).

If a resting-state EEG test is not clinically indicated, the AEP code (CPT 92585) can be used in place of the EEG code (CPT 95816).

The following CPT Codes are available to cover various portions of the COGNISION® test and subsequent analysis and evaluation. The availability of these codes does not guarantee reimbursement and the information in this table is for illustrative purposes only.

Procedure Codes		Common Disease Codes		Example Reimbursement*
CPT	***Description***	***ICD-10***	***Description***	***Rate***
92552	Pure tone audiometry	G30 G31	Alzheimer's disease Other neurodegenerative diseases	$32
95816	EEG 20-40 minutes			$374
95957**	EEG digital analysis	F01 F02	Vascular dementia Dementia in other diseases	$325
92585	Auditory evoked potentials for evoked response audiometry and/or testing of the central nervous system	F03 F04	Unspecified dementia Amnestic disorder	-
95212	EEG 41-60 minutes	S06.0X	Concussion	-
			Example Reimbursement Total	**$731**

* Reimbursement rates based on data from CMS. Current rates may be different.

** In Florida, a Medicare LCD (local coverage determination) limits the use of 95957 to cases of epilepsy and/or cerebral vascular disease. This code is reserved for advanced digital analysis, such as that performed using the COGNISION® Viewer application and is generally not applicable to spike detection alone. It is important to review any applicable LCDs for complete indications and limitations.

The availability of these codes does not guarantee reimbursement and the information in this table is for illustrative purposes only.

References:

[1] N. Mattsson *et al.*, "Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010.," *J. Neuropathol. Exp. Neurol.*, vol. 71, no. 4, pp. 266–73, Apr. 2012.

[2] S. Krishnamurti, R. Snell, B. King, and L. Drake, "Auditory Processing Deficits in Alzheimer's Disease," *Am. J. Alzheimer's Dis.*, no. 2013, pp. 1–11, 2013.

[3] G. A. Gates *et al.*, "Central auditory dysfunction in older persons with memory impairment or Alzheimer dementia.," *Arch. Otolaryngol. Head. Neck Surg.*, vol. 134, no. 7, pp. 771–7, Jul. 2010.

[4] J. W. Hall, "Auditory Processing Disorders: An Overview of Current Research James W. Hall III APD Series 2014 Auditory Processing Disorders (CAP/APD)," 2014.

[5] F. Vecchio *et al.*, "Resting state cortical EEG rhythms in Alzheimer's disease: toward EEG markers for clinical applications: a review.," *Suppl. Clin. Neurophysiol.*, vol. 62, pp. 223–36, Jan. 2013.

[6] W. Klimesch, "EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis.," *Brain Res. Brain Res. Rev.*, vol. 29, no. 2–3, pp. 169–95, Apr. 1999.

[7] S. J. Luck, *An Introduction to the Event-Related Potential Technique*. Cambridge, Massachusetts: The MIT Press, 2005.

[8] E. Katada, K. Sato, K. Ojika, and R. Ueda, "Cognitive Event-Related Potentials: Useful Clinical Information in Alzheimer's Disease," *Curr. Alzheimer Res.*, vol. 1, pp. 63–69, 2004.

[9] A. N. S. Institute, "Specification for audiometers (ANSI S3.6-1996)." American National Standards Institute, Inc., 1996.

[10] J. Polich and K. L. Herbst, "P300 as a clinical assay: rationale, evaluation, and findings.," *Int. J. Psychophysiol.*, vol. 38, no. 1, pp. 3–19, Oct. 2000.

[11] J. Polich and J. Corey-bloom, "Alzheimer's Disease and P300: Review and Evaluation of Task and Modality," *Curr. Alzheimer Res.*, vol. 300, no. 2, pp. 515–525, 2005.

[12] E. Golob and A. Starr, "Effects of stimulus sequence on event-related potentials and reaction time during target detection in Alzheimer's disease," *Clin. Neurophysiol.*, vol.

111, no. 8, pp. 1438–1449, Aug. 2000.

[13] S. Yamaguchi, H. Tsuchiya, S. Yamagata, G. Toyoda, and S. Kobayashi, "Event-related brain potentials in response to novel sounds in dementia," *Clin. Neurophysiol.*, vol. 111, no. 2, pp. 195–203, Feb. 2000.

[14] M. Cecchi *et al.*, "A clinical trial to validate ERP markers of Alzheimer' s disease in outpatient settings," *Alzheimer's Dement. Diagnosis, Assess. Dis. Monit.*

[15] E. Golob *et al.*, "Cortical event-related potentials in preclinical familial Alzheimer disease," *Neurology*, vol. 73, no. 20, pp. 1649–1655, Nov. 2009.

[16] N. Boutros, M. W. Torello, E. M. Burns, S. S. Wu, and H. A. Nasrallah, "Evoked potentials in subjects at risk for Alzheimer's disease.," *Psychiatry Res.*, vol. 57, no. 1, pp. 57–63, Jun. 1995.

[17] E. J. Golob, R. Irimajiri, and A. Starr, "Auditory cortical activity in amnestic mild cognitive impairment: relationship to subtype and conversion to dementia.," *Brain*, vol. 130, no. Pt 3, pp. 740–52, Mar. 2007.

[18] H. Davis, T. Mast, N. Yoshie, and S. Zerlin, "The slow response of the human cortex to auditory stimuli: recovery process.," *Electroencephalogr. Clin. Neurophysiol.*, vol. 21, no. 2, pp. 105–13, Aug. 1966.

[19] J. M. Olichney *et al.*, "Abnormal verbal event related potentials in mild cognitive impairment and incipient Alzheimer's disease," *J. Neurol. Neurosurg. Psychiatry*, vol. 73, no. 4, pp. 377–384, 2002.

[20] M. Spreng, "Influence of impulsive and fluctuating noise upon physiological excitations and short-time readaptation.," *Scand. Audiol. Suppl.*, no. Suppl 12, pp. 299–306, Aug. 1980.

[21] E. Golob and A. Starr, "Age-related qualitative differences in auditory cortical responses during short-term memory," *Clin. Neurophysiol.*, vol. 111, no. 12, pp. 2234–2244, Dec. 2000.

[22] S. A. Hillyard, R. F. Hink, V. L. Schwent, and T. Picton, "Electrical Signs of Selective Attention in the Human Brain," *Science,* vol. 182, no. 4108, pp. 177–180, 1973.

[23] S. E. Arnold, B. T. Hyman, J. Flory, A. R. Damasio, and G. W. Van Hoesen, "The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease.," *Cereb. Cortex*, vol. 1, no. 1, pp. 103–16, Jan. 1991.

[24] G. E. Alexander, J. D. Newman, and D. Symmes, "Convergence of prefrontal and acoustic inputs upon neurons in the superior temporal gyrus of the awake squirrel monkey.," *Brain Res.*, vol. 116, no. 2, pp. 334–8, Nov. 1976.

[25] R. Metherate and J. H. Ashe, "Nucleus basalis stimulation facilitates thalamocortical synaptic transmission in the rat auditory cortex.," *Synapse*, vol. 14, no. 2, pp. 132–43, Jun. 1993.

[26] A. P. Key, G. O. Dove, and M. J. Maguire, "Linking brainwaves to the brain: an ERP primer," *Dev. Neuropsychol.*, vol. 27, no. 2, pp. 183–215, Jan. 2005.

[27] A. Hampton and C. Weber-Fox, "Non-linguistic auditory processing in stuttering: evidence from behavior and event-related brain potentials.," *J. Fluency Disord.*, vol. 33, no. 4, pp. 253–73, Dec. 2008.

[28] S. H. Patel and P. N. Azzam, "Characterization of N200 and P300: selected studies of the Event-Related Potential.," *Int. J. Med. Sci.*, vol. 2, no. 4, pp. 147–154, Jan. 2005.

[29] K. Bennys, F. Portet, and J. Touchon, "Diagnostic Value of Event-Related Evoked Potentials N200 and P300 Subcomponents in Early Diagnosis of Alzheimer's Disease and Mild Cognitive Impairment," *J. Clin. Neurophysiol.*, vol. 24, no. 5, pp. 405–412, 2007.

[30] V. T. Papaliagkas, V. K. Kimiskidis, M. N. Tsolaki, and G. Anogianakis, "Cognitive event-related potentials: longitudinal changes in mild cognitive impairment.," *Clin. Neurophysiol.*, vol. 122, no. 7, pp. 1322–1326, Jul. 2011.

[31] J. Polich, "Updating P300: an integrative theory of P3a and P3b.," *Clin. Neurophysiol.*, vol. 118, no. 10, pp. 2128–2148, Oct. 2007.

[32] A. M. Fjell and K. B. Walhovd, "P300 and neuropsychological tests as measures of aging: scalp topography and cognitive changes," *Brain Topogr.*, vol. 14, no. 1, pp. 25–40, Jan. 2001.

[33] F. Vecchio and S. Määttä, "The use of auditory event-related potentials in Alzheimer's disease diagnosis.," *Int. J. Alzheimers. Dis.*, vol. 2011, pp. 1–7, Jan. 2011.

[34] S. Baudic, G. D. Barba, M. C. Thibaudet, A. Smagghe, P. Remy, and L. Traykov, "Executive function deficits in early Alzheimer's disease and their relations with episodic memory," *Arch. Clin. Neuropsychol.*, vol. 21, no. 1, pp. 15–21, 2006.

[35] R. J. Caselli *et al.*, "Longitudinal modeling of frontal cognition in APOE ε4 homozygotes, heterozygotes, and noncarriers," *Neurology*, vol. 76, no. 16, pp. 1383–1388, 2011.

[36] Y. Y. Lim *et al.*, "Effect of amyloid on memory and non-memory decline from preclinical to clinical Alzheimer's disease," *Brain*, vol. 137, no. 1, pp. 221–231, 2014.

[37] E. Donchin and M. G. H. Coles, "Is the P300 component a manifestation of context updating?," *Behav. Brain Sci.*, vol. 11, no. 03, p. 357, Feb. 1988.

[38] C. C. Duncan-Johnson and E. Donchin, "The P300 component of the event-related brain potential as an index of information processing," *Biol. Psychol.*, vol. 14, no. 1, pp. 1–52, 1982.

[39] M. Kutas, G. McCarthy, and E. Donchin, "Augmenting mental chronometry: the P300 as a measure of stimulus evaluation time.," *Science*, vol. 197, no. 4305, pp. 792–5, Aug. 1977.

[40] D. S. Ruchkin, R. Johnson, D. Mahaffey, and S. Sutton, "Toward a functional categorization of slow waves," *Psychophysiology*, vol. 25, no. 3, pp. 339–53, May 1988.

[41] E. Angelakis, J. F. Lubar, S. Stathopoulou, and J. Kounios, "Peak alpha frequency: an electroencephalographic measure of cognitive preparedness.," *Clin. Neurophysiol.*, vol. 115, no. 4, pp. 887–97, Apr. 2004.

[42] I. Raicher, D. Y. Takahashi, P. Afonso, M. Kanda, R. Nitrini, and R. Anghinah, "qEEG spectral peak in Alzheimer ' s disease A possible tool for treatment follow-up," vol. 2, no. 1, pp. 9–12, 2008.

[43] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, and E. M. Stadlan, “Clinical diagnosis of Alzheimer’s Disease - Report of the NINCDS-ADRDA Work Group under the auspices of Dept of HHS Task Force on AD,” *Neurology*, vol. 34, pp. 939–944, 1984.

[44] M. Nuwer, “Assessment of digital EEG, quantitative EEG, and EEG brain mapping: Report of the American Academy of Neurology and the American Clinical Neurophysiology Society,” *Neurology*, vol. 49, no. 1, pp. 277–292, Jul. 1997.

[45] Alzheimer’s Association, “FAQ on New Guidelines for Alzheimer’s Disease Diagnosis,” April. 2011.

[46] E. Gordon, C. Kraiuhin, A. Harris, R. Meares, and A. Howson, “The differential diagnosis of dementia using P300 latency.,” *Biol. Psychiatry*, vol. 21, no. 12, pp. 1123–32, Oct. 1986.

[47] J. V Patterson, H. J. Michalewski, and A. Starr, “Latency variability of the components of auditory event-related potentials to infrequent stimuli in aging, Alzheimer-type dementia, and depression.,” *Electroencephalogr. Clin. Neurophysiol.*, vol. 71, no. 6, pp. 450–60, 1988.

[48] W. S. Brown, J. T. Marsh, and A. LaRue, “Event-related potentials in psychiatry: differentiating depression and dementia in the elderly.,” *Bull. Los Angeles Neurol. Soc.*, vol. 47, pp. 91–107, Jan. 1982.

[49] L. Bonanni *et al.*, “Revisiting P300 cognitive studies for dementia diagnosis: Early dementia with Lewy bodies (DLB) and Alzheimer disease (AD).,” *Neurophysiol. Clin.*, vol. 40, no. 5–6, pp. 255–65, 2010.

[50] “Early Detection | Public Health | Alzheimer’s Association.” [Online]. Available: http://alz.org/publichealth/early-detection.asp. [Accessed: 15-May-2015].

[51] Y. T. Quiroz *et al.*, “Event-related potential markers of brain changes in preclinical familial Alzheimer disease,” *Neurology*, vol. 77, no. 5, pp. 469–475, Aug. 2011.

[52] J. M. Olichney *et al.*, “Patients with MCI and N400 or P600 abnormalities are at very high risk for conversion to dementia.,” *Neurology*, vol. 70, no. 19 Pt 2, pp. 1763–1770, May 2008.

[53] K. C. Fadem *et al.*, “A Multi-Center Clinical Trial to Validate Event-Related Potentials as Useful Biomarkers for Early Detection of Alzheimer’s disease.,” *Oral Present. CTAD Conf. Monte Carlo, Monaco.*, 2012.

[54] D. L. Green, L. Payne, R. Polikar, P. J. Moberg, D. A. Wolk, and J. Kounios, “P50: A candidate ERP biomarker of prodromal Alzheimer’s disease.,” *Brain Res.*, vol. 1624, pp. 390–397, Aug. 2015.

[55] K. Bennys, G. Rondouin, E. Benattar, A. Gabelle, and J. Touchon, “Can event-related potential predict the progression of mild cognitive impairment?,” *J. Clin. Neurophysiol.*, vol. 28, no. 6, pp. 625–632, Dec. 2011.

[56] C.-L. Lai, R.-T. Lin, L. M. Liou, and C.-K. Liu, “The role of event-related potentials in cognitive decline in Alzheimer’s disease.,” *Clin. Neurophysiol.*, vol. 121, no. 2, pp. 194–9, Feb. 2010.

[57] M. Penttilä, J. V Partanen, H. Soininen, and P. J. Riekkinen, “Quantitative analysis of occipital EEG in different stages of Alzheimer’s disease.,” *Electroencephalogr. Clin. Neurophysiol.*, vol. 60, no. 1, pp. 1–6, Jan. 1985.

[58] a E. Werber, C. Klein, and J. M. Rabey, “Evaluation of cholinergic treatment in demented patients by P300 evoked related potentials.,” *Neurol. Neurochir. Pol.*, vol. 35 Suppl 3, pp. 37–43, Jan. 2001.

[59] M. Onofrj *et al.*, “Donepezil Versus Vitamin E in Alzheimer’s Disease Part 2 : Mild Versus Moderate – Severe Alzheimer’s Disease,” *Clin. Neuropharmacol.*, vol. 25, no. 4, pp. 207–215, 2002.

[60] M. Takano *et al.*, “Effects of Memantine on Event-Related Potentials in Alzheimer’s Disease Under Donepezil Treatment,” *Neurosci. Biomed. Eng.*, vol. 1, no. 1, pp. 34–39, May 2013.

[61] G. Rodriguez, P. Vitali, C. De Leo, F. De Carli, N. Girtler, and F. Nobili, “Quantitative EEG changes in Alzheimer patients during long-term donepezil therapy.,” *Neuropsychobiology*, vol. 46, no. 1, pp. 49–56, Jan. 2002.