Virtual KOL Event: Reviewing the Predictive Nature of P300 in Determining the Clinical Benefit of Alzheimer's Disease Treatments

with Dr. Larry Ereshefsky

October 28, 2020

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This presentation concerns drug candidates that are under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration. The drug candidates are currently limited by federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

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Dr. Larry Ereshefsky

Larry Ereshefsky, PharmD, BCPP, FCCP leverages his over 45 years experience as a clinician, scientist and investigator to develop treatments and innovate clinical methodologies to make a difference in the lives of patients with neurodegenerative and psychiatric disorders. He has contributed significantly to several drug approvals spanning neurology and psychiatry, including drug development planning, PK/PD evaluation, and methodological innovation for Parkinson's (PD), Alzheimer's Diseases (AD), chronic and acute pain models, as well as numerous psychiatric indications including schizophrenia, TRD, bipolar and anxiety disorders.

Dr. Ereshefsky is a retired Regents Professor of Pharmacy, Psychiatry, and Pharmacology from The University of Texas/UT Health Science Center (UT). He has been a leader in the application of translational drug development tools including neurocircuitry/biomarker based (RDoC) strategies, i.e., continuous CSF sampling, QEEG, ERP, PSG, sMRI, fMRI, MRS, PET, pain models including capsaicin, UV burn, NGF, allodynia evaluations, and cognitive and behavioral paradigms.

He served twice on the FDA Psychopharmacological Drugs Advisory Committee. His PharmD and Residency in Psychopharmacology and Clinical Pharmacy were at the University of Southern California and LA County Medical Center. He is also a founding advisory board member and consultant to the ERP Biomarker Qualification Consortium.

Agenda

- Athira corporate overview
  - *Leen Kawas*
- Introduction to P300
  - *Larry Ereshefsky*
- Video demonstration of P300
- Background on P300 and its utility as a functional measurement of cognition
  - *Larry Ereshefsky*
- Clinical results from completed trials of ATH-1017 in individuals with Alzheimer’s disease and ongoing trials
  - *Leen Kawas*
- Question & answer session with analysts

Overview of Athira Pharma

Pipeline focused on regeneration of neuronal damage in CNS and peripheral diseases to restore function

ATH-1017 LEAD INDICATION:
Alzheimer's disease

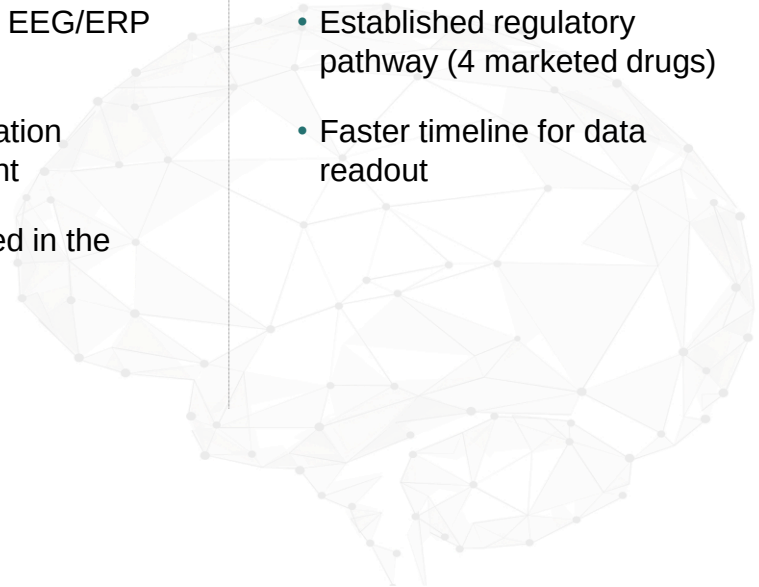
POTENTIAL FOLLOW-ON INDICATIONS:
Parkinson's dementia, ALS, MS, neuropathy, and neuropsychiatric etc. (additional compounds in development)

Lead asset ATH-1017 with novel regenerative MOA

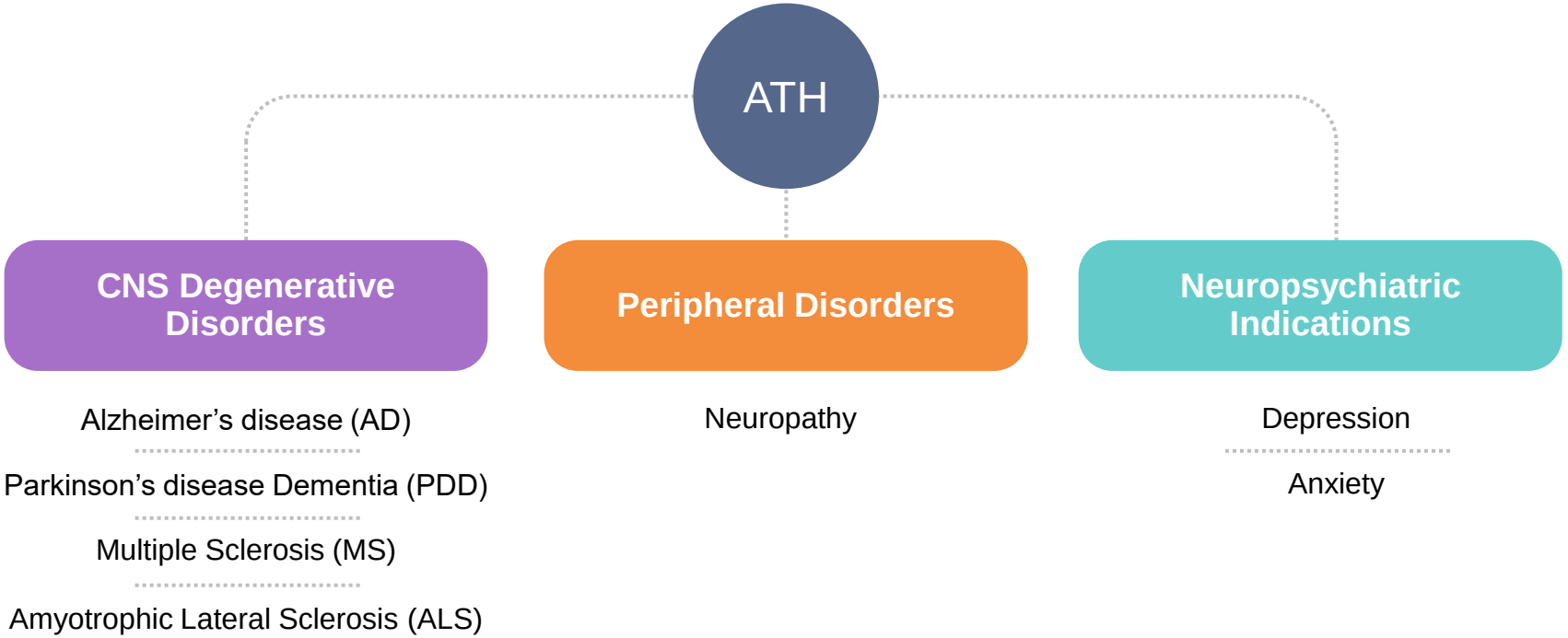
- Encouraging data in AD subjects (double blind study)
- Rapid improvement in EEG/ERP P300 latency
- Supports CNS penetration and target engagement
- Generally well-tolerated in the Phase 1 a/b

Efficient Clinical development strategy

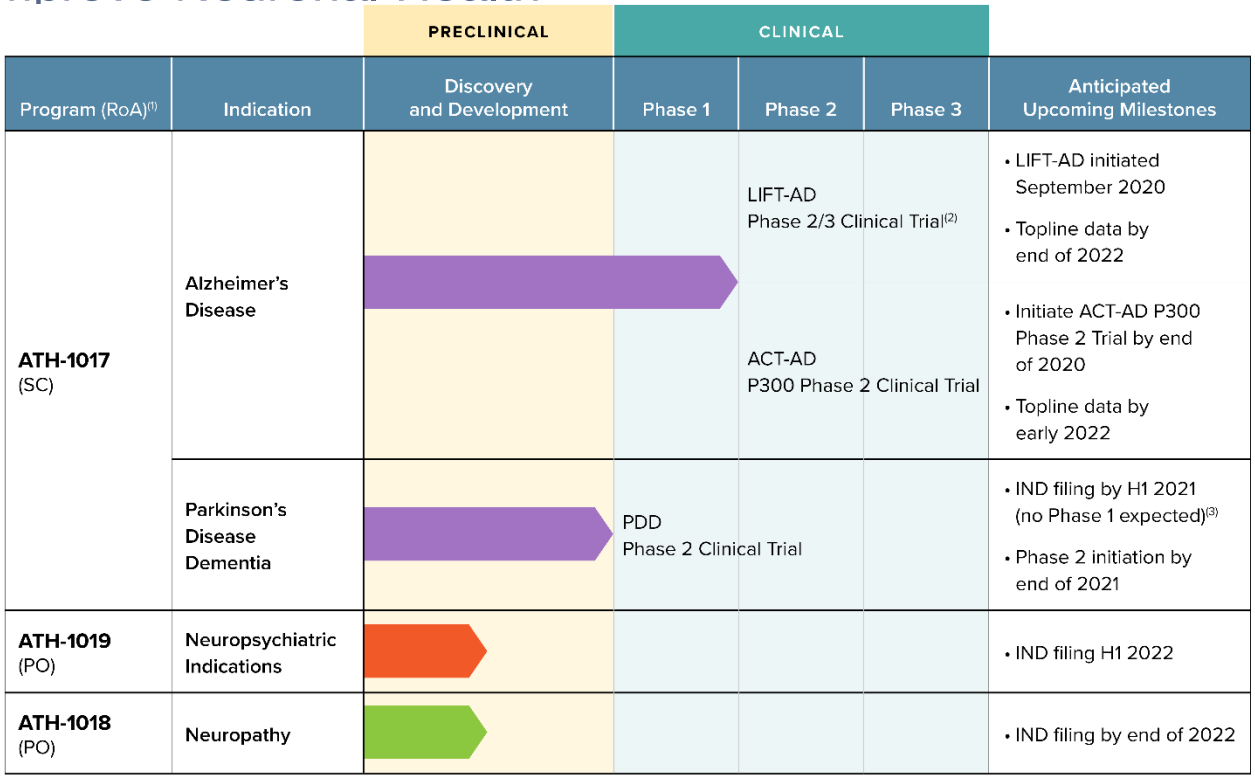
- Cost and time efficient clinical trials
- Established regulatory pathway (4 marketed drugs)
- Faster timeline for data readout



ATH Compounds Have Therapeutic Potential in a Broad Range of Clinical Applications



Current Development Stage of ATH Compounds and Discovery Research Programs to Improve Neuronal Health

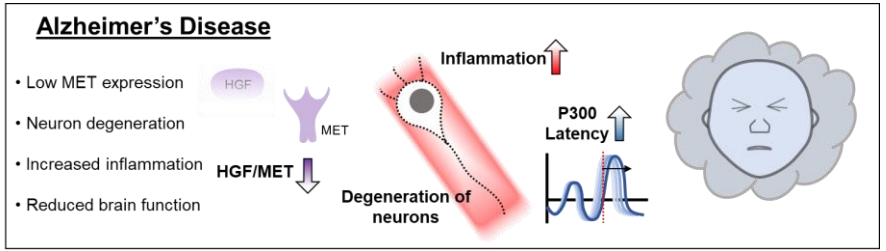


(1) RoA: route of administration; SC: subcutaneous; PO: oral.
(2) ATH-1017 for AD is moving from Phase 1b to a Phase 2/3 clinical trial that may provide pivotal data in support of registration based on discussions with FDA.
(3) We plan to initiate a Phase 2 clinical trial in PDD based on results from Phase 1a and 1b clinical trials in AD with ATH-1017. A second IND for PDD can cross-reference the already active IND for AD. It is not required that we repeat any studies or trials that are applicable across the two indications for the second IND for PDD, including a Phase 1 clinical trial.

Athira's Target, HGF/MET, is a Vital Neuronal Growth Factor that Promotes Neuronal Health and Regeneration

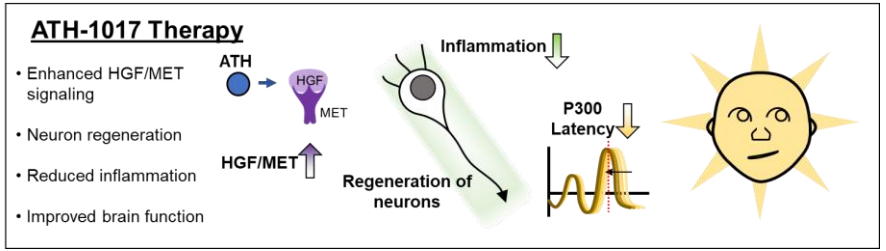
Hepatocyte* Growth Factor (HGF)/MET Receptor

- **Critical to neuron function, learning, and memory**
- **Gene expression is reduced in Alzheimer's**
- **Multi-modal beneficial mechanism of action**



Demonstrated Effects of HGF/MET in Animal Models

- **Alleviation of Aβ-induced cognitive impairment**
- **Prevention of onset of Parkinson's disease**
- **Prolongs life span in a transgenic mouse model of ALS**
- **Improved learning and memory dysfunction of microsphere-embolized rats**



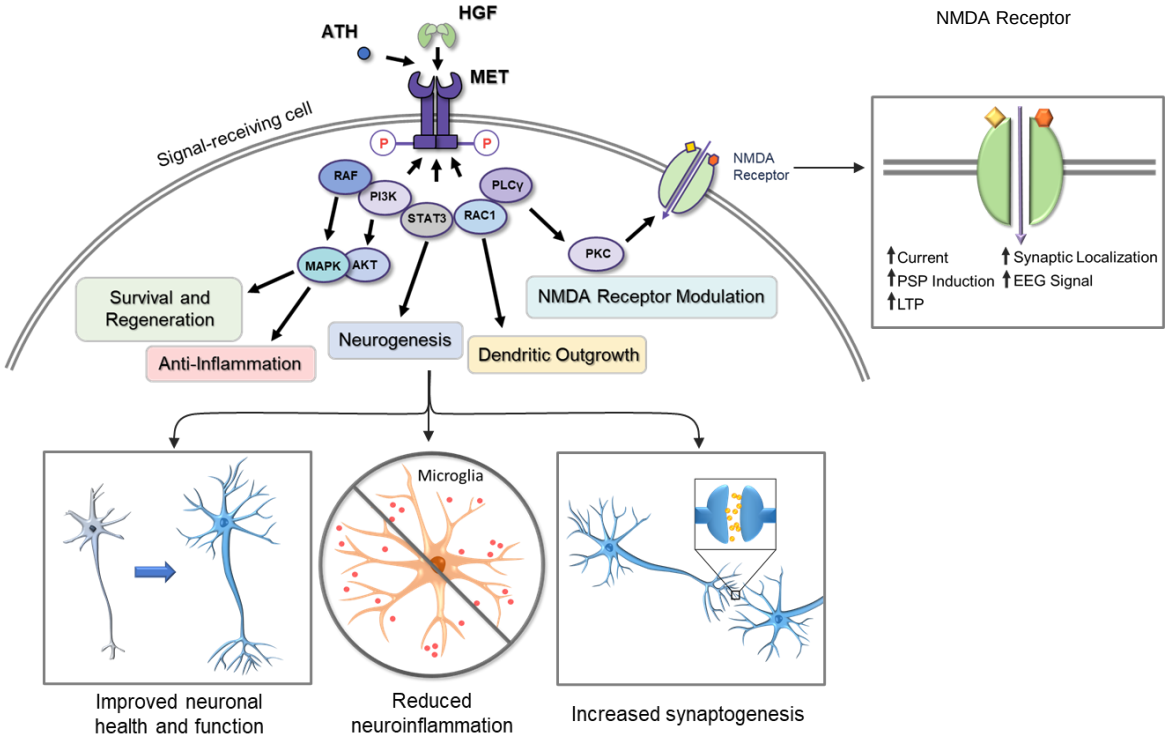
*Historically termed

HGF/MET Enhances and Improves Key Neuronal Receptor Activity

Acute and Sustained Effects on Synaptic and Network Function

- Fast-acting positive modulator
- **Protective and regenerative**
- **Procognitive (Symptomatic)**
- EEG measure

ATH-1017 Is Designed to Enhance HGF/MET



Introduction to Evoked-Response Potential (ERP)

Introduction to Evoked-Response Potential (ERP)

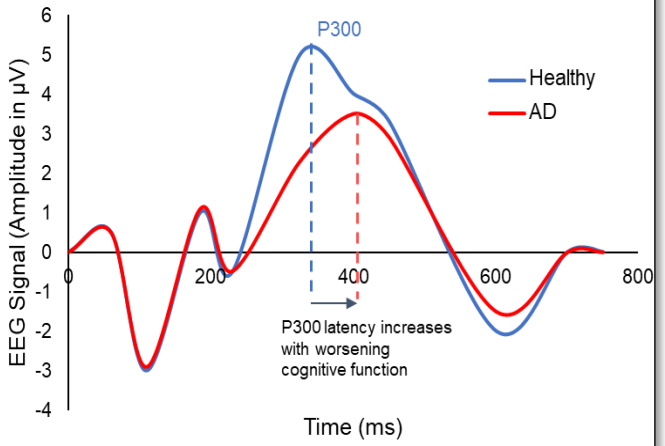
Dr. Larry Ereshefsky, PharmD, BCPP, FCCP
CSO, Apex Innovative Sciences
Follow the Molecule CNS Consulting

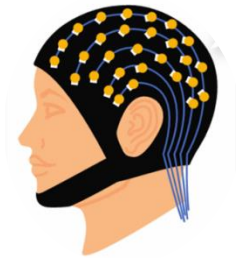
EEG Measures Electrical Activity from Firing Neurons in the Brain

EVENT RELATED POTENTIALS (ERP): P300 Latency

- Functional measurement for working memory access and executive function
- Strongly suggestive of memory improvement

Pathological changes in P300 latency correlate with cognitive impairment





EEG records brain electrical activity from electrodes placed on the scalp

QUANTITATIVE EEG (qEEG)

- Translational tool from rodents to humans
- PK/PD modeling for dose selection

Noninvasive EEG recordings reflect brain activity and function

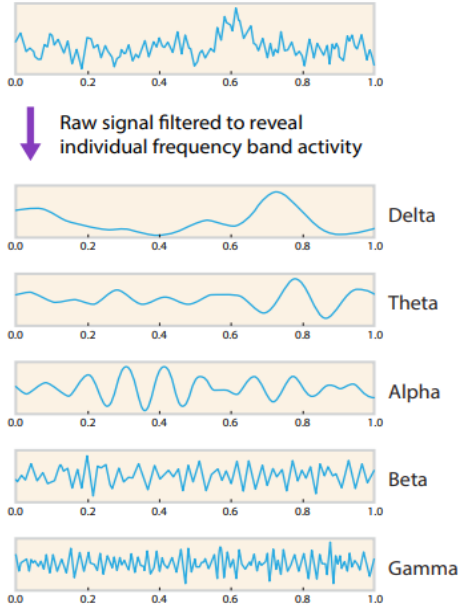
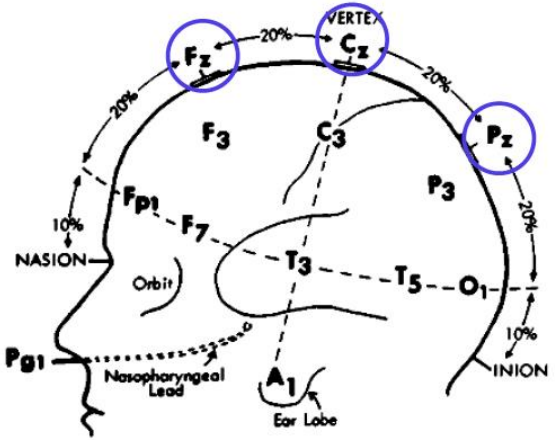
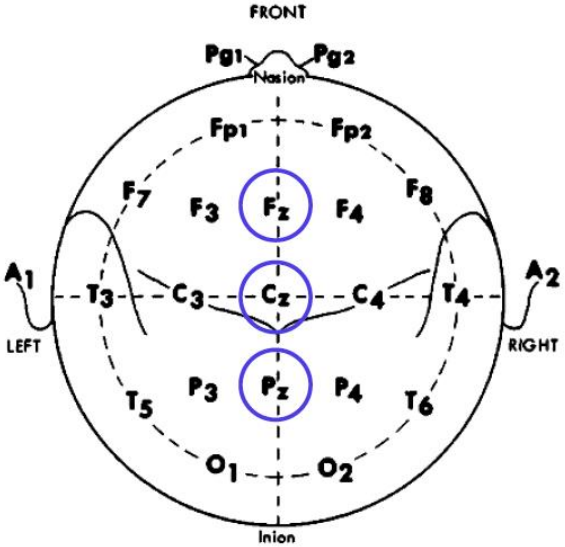


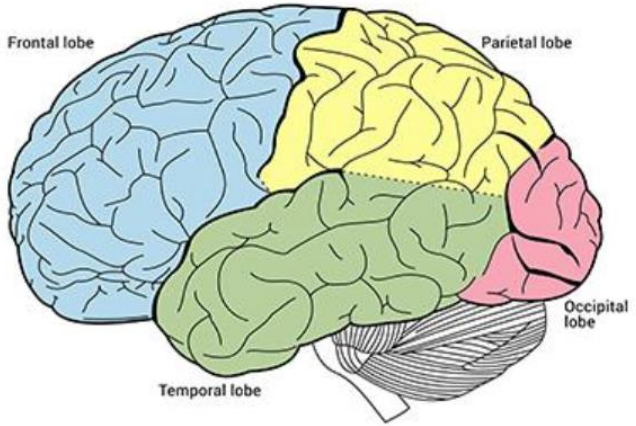
Diagram of Standard 10-20 Montage: Electrode Placement on Scalp



LEFT SIDE OF HEAD



TOP OF HEAD

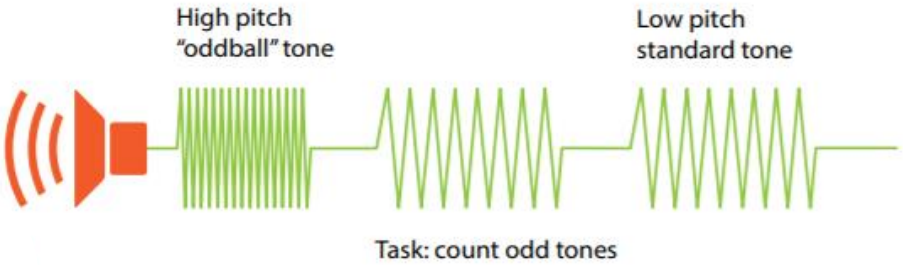


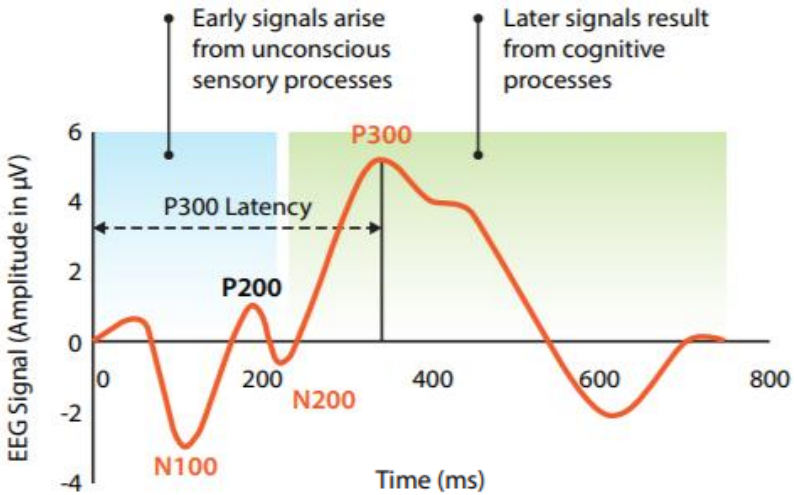
Midline structures (circled) considered most relevant for ERP

- Frontal Fz
- Frontal Parietal CZ
- Parietal Regions Pz

Auditory ERP Paradigm

- Task is to count the “oddball” tones
- A P300 wave is generated in response to the “oddball” tone
- Repetition is key, the more trials the better the data quality
- Phase-locked responses to a target “oddball” tone are averaged to produce an ERP waveform



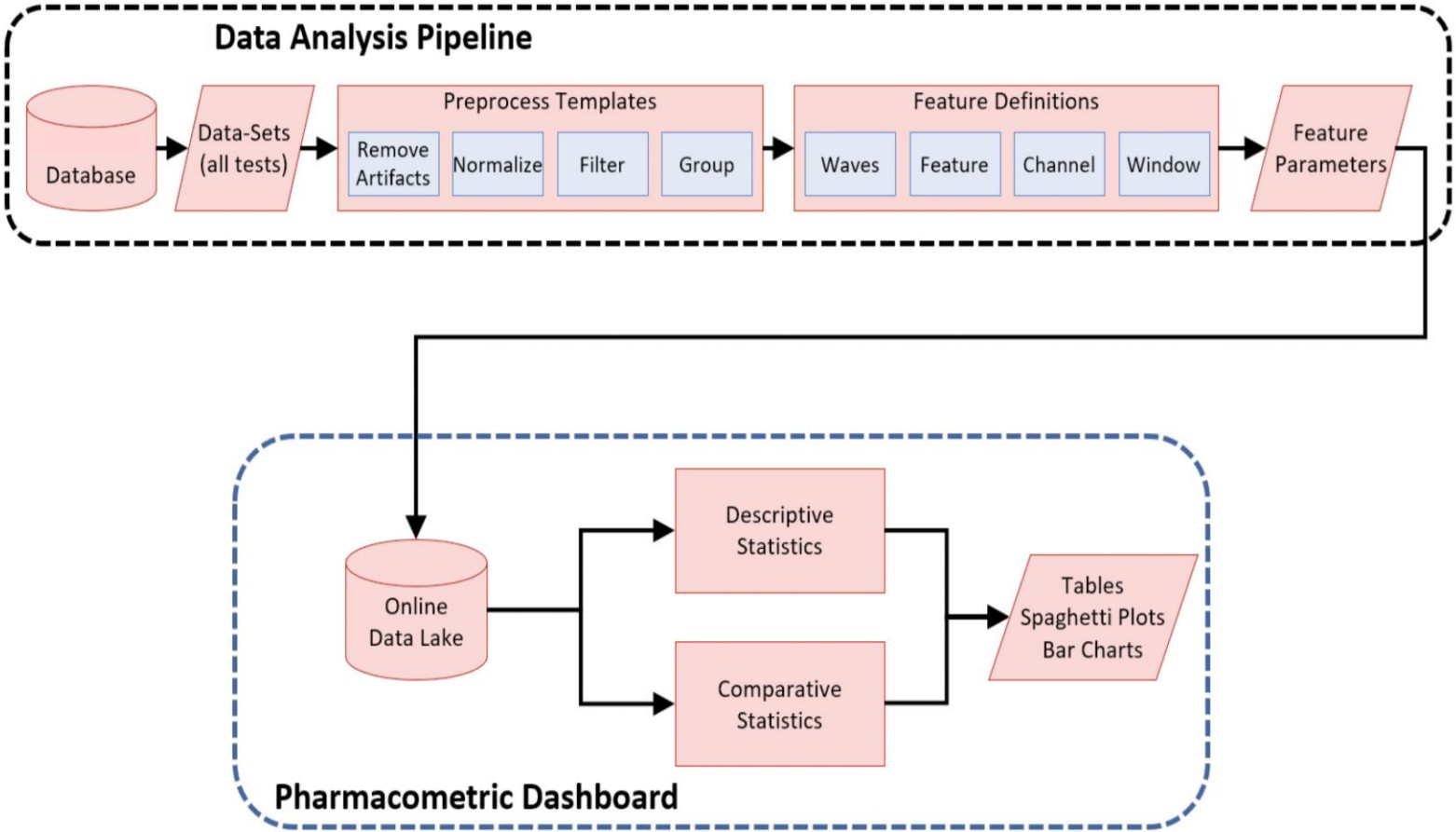


Working Memory Access

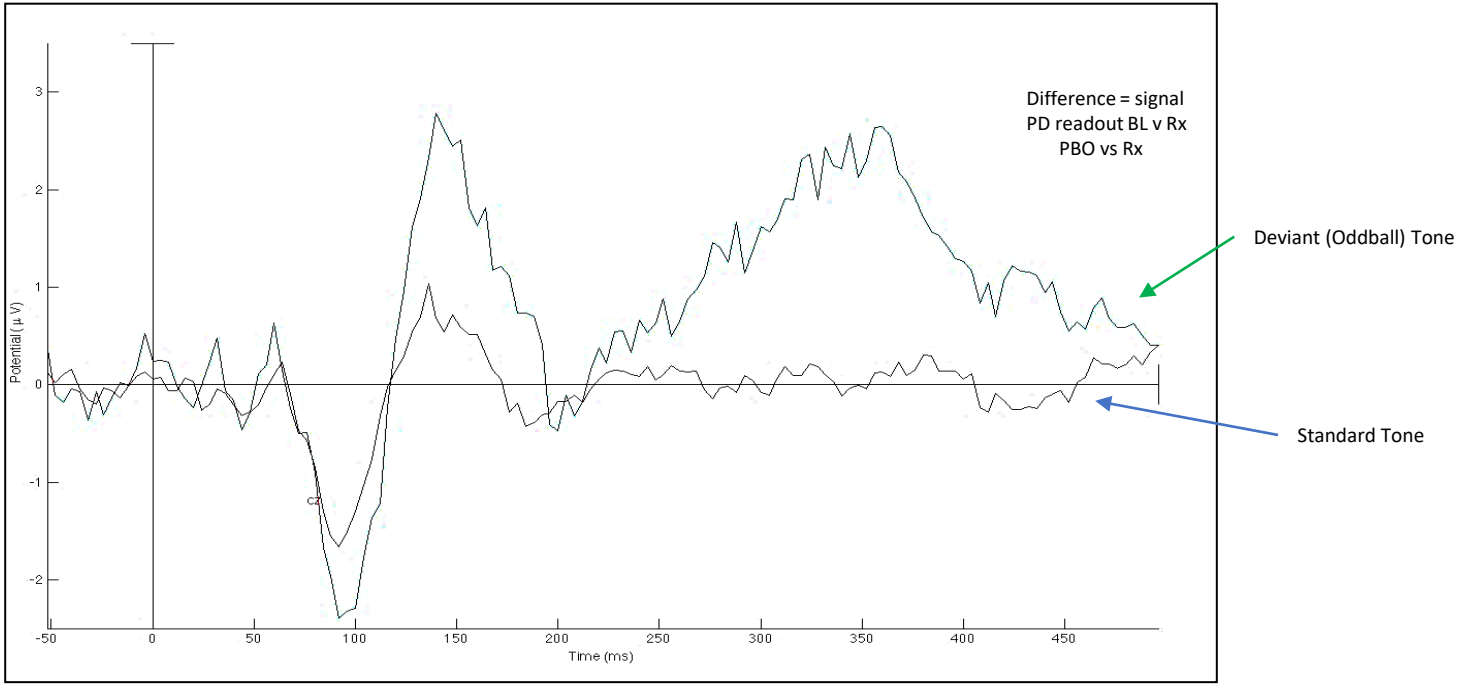
Pre-attentional **Emotional Processing**

Video

ERP Data Processing Flow

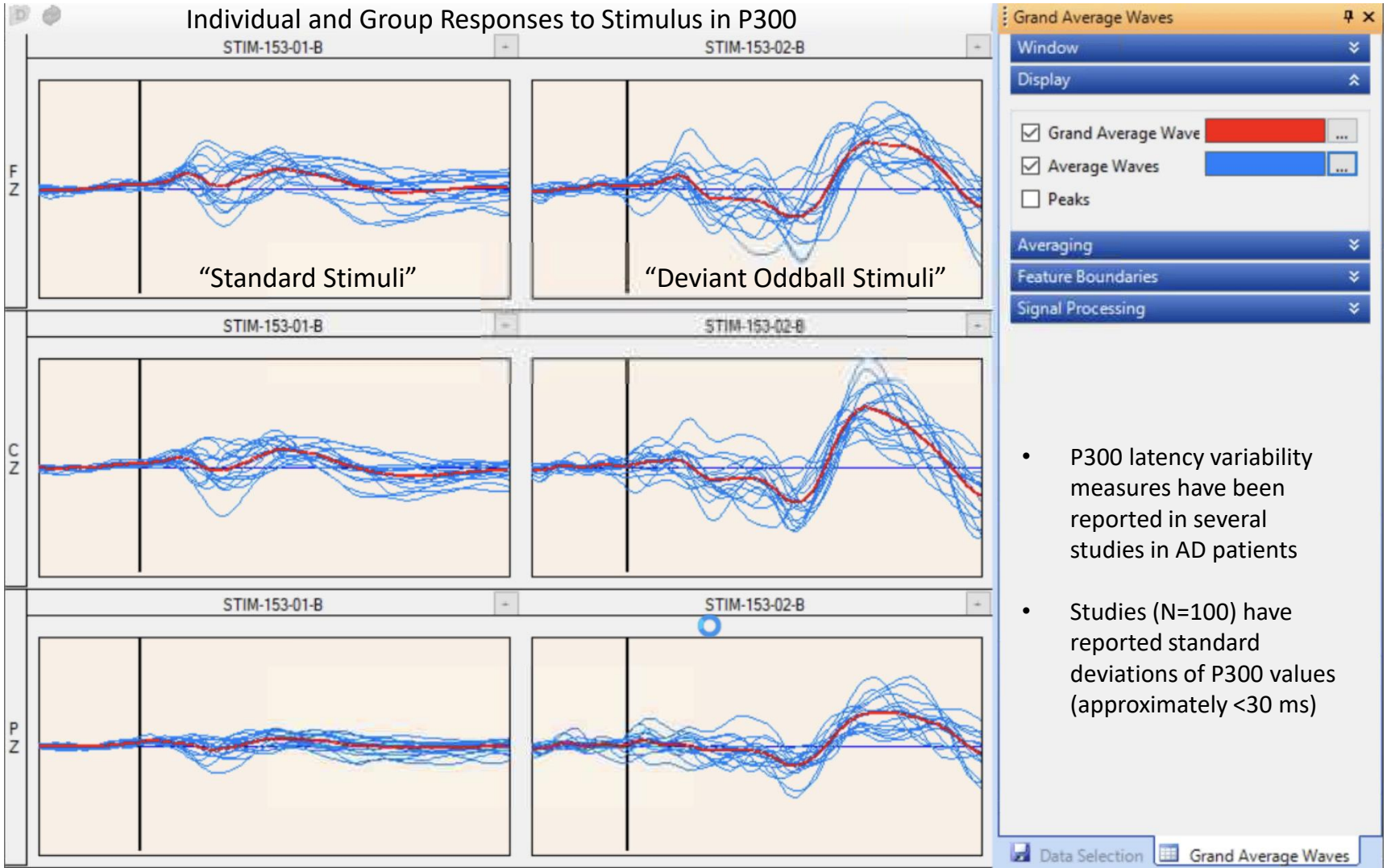


Cognitive ERP Relation to Memory Function: Auditory P300 – 10-20 lead system Qmetrx Acquisition at Hassman Research Institute (Ereshefsky)



Averaged P300 waveforms from the vertex midline (Cz, referenced to midtemporal sites (T7,T8). *Note that the deviant tone produces a sustained positivity over the 250-450 msec range with a robust peak at 350 msec.

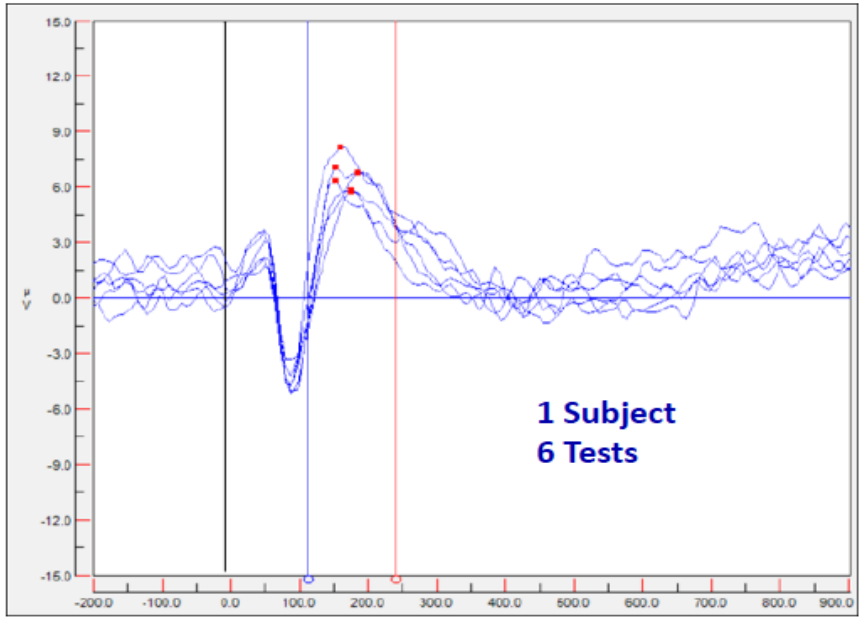
Responses to approximately 80 deviant and 240 standard stimuli averaged in one subject



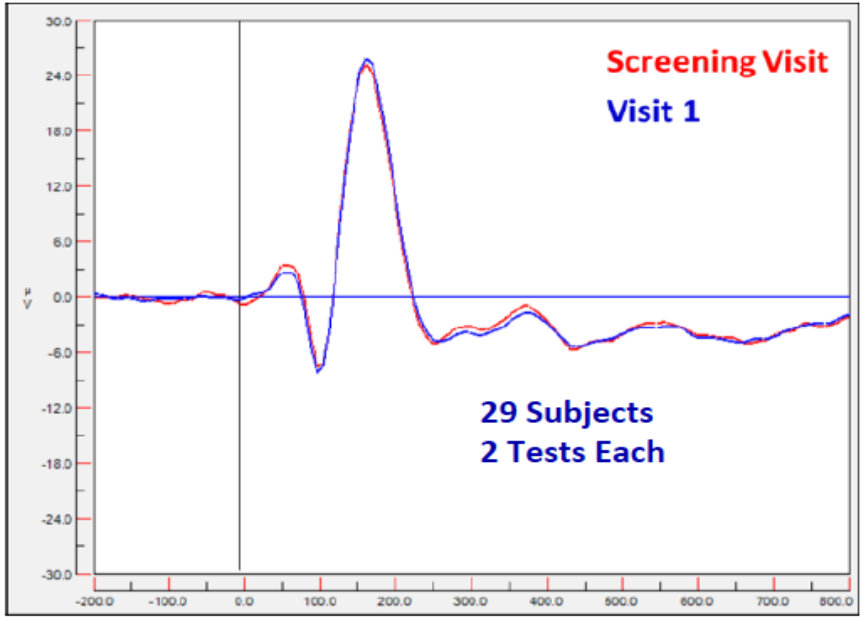
- P300 latency variability measures have been reported in several studies in AD patients
- Studies (N=100) have reported standard deviations of P300 values (approximately <30 ms)

Test and Retest Reliability of ERP Data Collected by Cognision Consortium *(CNS Network and Hassman Research Institute, Ereshefsky CSO)*

Intra-subject



Group

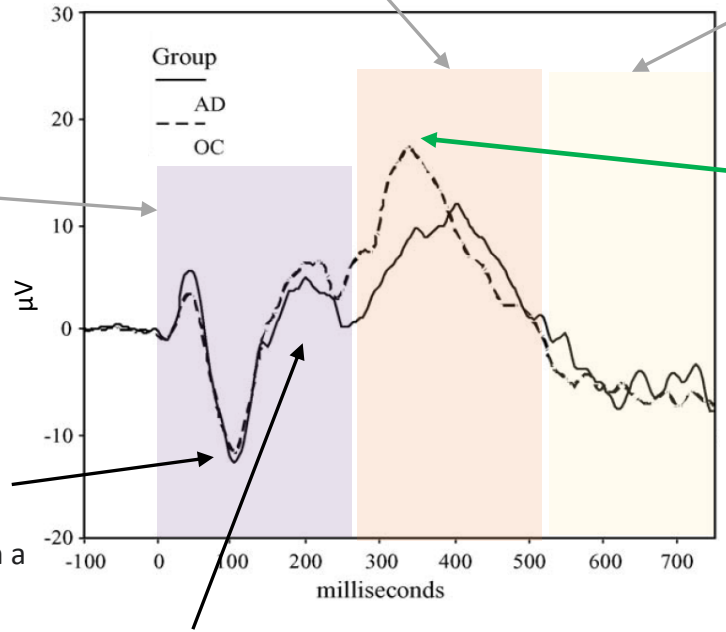


Event Related Potential Signal Processing

Working memory access

Emotional processing

Pre-attentional



P300
- Immediate cognitive processing of the event
- Relies on working memory, higher functions
- Is highly influenced by dementia
- Latency increases in AD patients
  - Patients are slower to access working memory as a result of decreased synaptic transmission

N100
- Pre-attentive perception
- Amplitude proportional to frequency differential from a preceding tone

P200
- Aspects of higher-order perceptual processing
- Modulated by attention
- Multi-factoral elements contribute, frequently analyzed as the N1-P2 complex

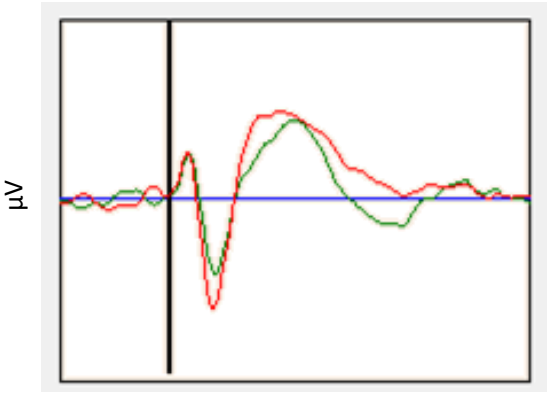
Adapted from Ally et al, 2006

ERP in Alzheimer's: a Synaptic Measure for a Synaptic Disease

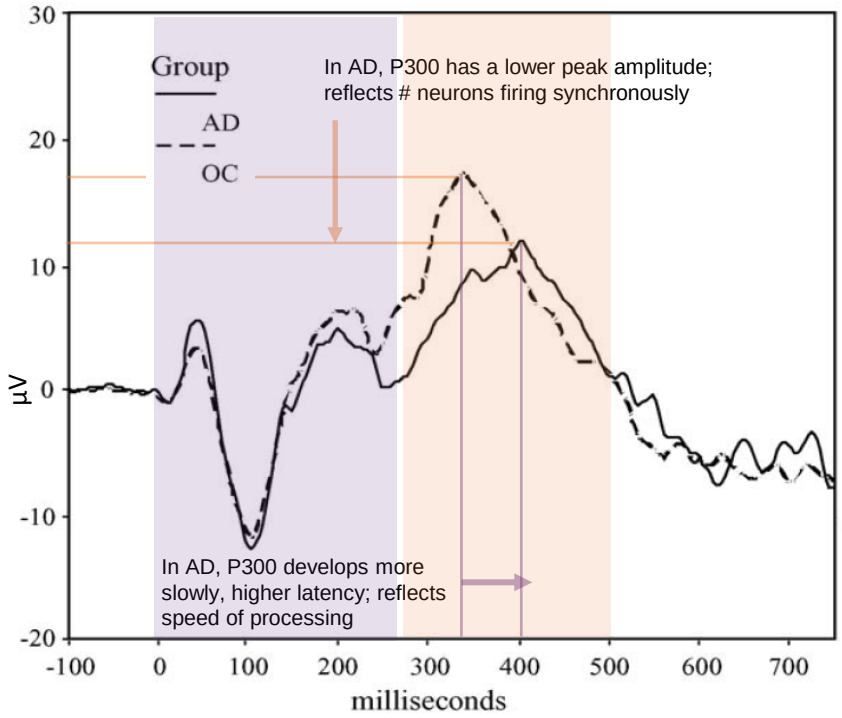
- Regardless of the root cause of AD, the cognitive symptoms represent a widespread loss of synaptic input caused by degeneration of neurons
- Event-related potentials (ERPs) directly measure the speed and strength of cognitive processing (Olichney et al, 2011)
- ERP signals erode during normal aging –This process is further accelerated in dementia patients
- Many studies have discriminated between healthy elderly and AD cohorts based on ERP waveform morphology –as early as published reports from 1980s

Active Oddball

Age-matched Healthy (57) v AD (44)



ERP in Alzheimer's Disease



- Many studies have identified differences in P300 in AD and MCI
- P300 latency more consistent than amplitude reduction
- Fewer subjects yield significant and reproducible amplitude reduction

Study	Population (n)	Electrode placement	P300 Latency	P300 Amplitude
Caravaglios et al., 2008	HC (16) AD (21)	Fz, Cz and Pz	AD > HC	--
O'Mahony et al., 1996	HC (20) AD (18)	Fz, Cz and Pz	AD > HC	--
Lai et al., 2010	HC (16) AD (16)	Fz, Cz and Pz	AD > HC	--
Yamaguchi et al., 2000	HC (16) AD (16)	Cz and Pz	AD > HC	HC > AD
Golob and Starr, 2000	HC (12) AD (10)	Fz, Cz and Pz	AD > HC	HC > AD
Bennys et al., 2007	HC (10) MCI (20) AD (30)	Fz, Cz and Pz	AD > MCI > HC	HC > MCI = AD
Juckel et al., 2008	HC (16) AD (18)	32 channels	AD > HC	HC > AD
Frodl et al., 2002	HC (26) MCI (26) AD (30)	29 channels	AD > MCI > HC	HC > MCI = AD
Ally et al., 2006	HC (80) AD (80)	10-20	AD > HC	HC > AD
Cecchi et al., 2015	HC (101) Mild AD (103)	Fz, Cz, Pz, F3, P3, F4, and P4	AD > HC	HC > AD

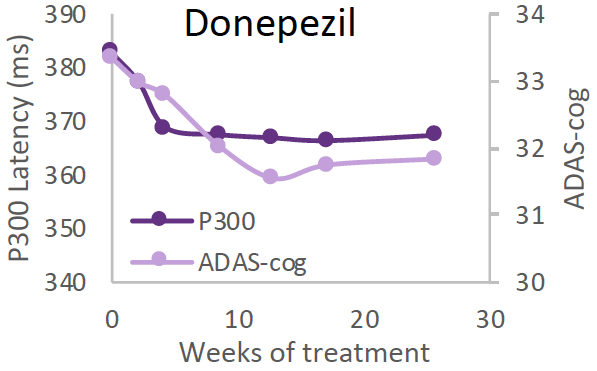
Figure adapted from Ally et al, 2006

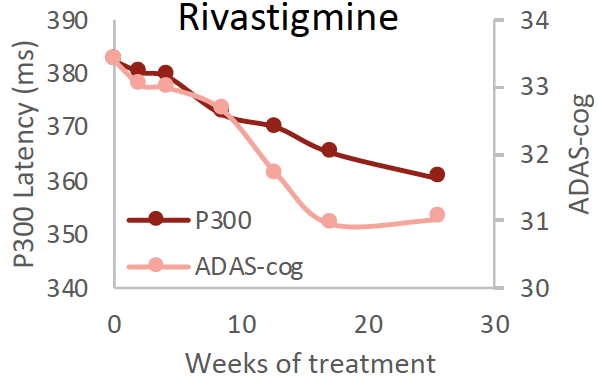
P300 Latency v Amplitude Measurements for Drug Response

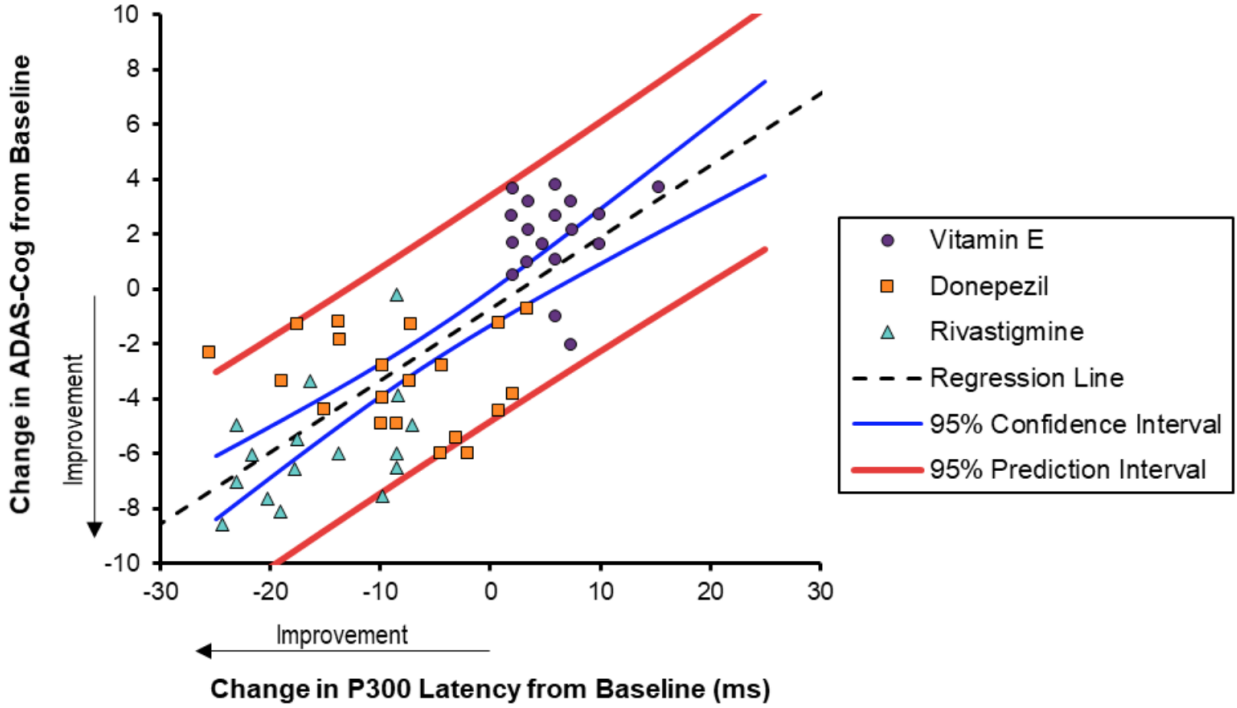
- Small molecules with a range of neuroactive mechanisms can influence cognitive performance
- The pharmacodynamics of these drugs has been clearly detected by changes in P300 latency
- Changes in P300 amplitude are less sensitive to procognitive therapeutics

			ERP Effects		
Treatment	**Population**	**Cognitive Effects**	**P300 Latency**	**P300 Amplitude**	**References**
Donepezil (AChEI)	Alzheimer's	Improved ADAS-cog scores	Significant improvement	Inconsistent - No effect in Katada study; significant improvement in Thomas study but was not correlated to cognition at baseline	Katada et al., 2003 Thomas et al., 2001
Modafinil	Sleep deprivation	Improved cognition and alertness after sleep deprivation	Significant improvement	Inconsistent - Increased at only one electrode site (Yaman); no effect in Saletu study	Yaman et al., 2015 Saletu et al., 2009
Valsartan	Hypertension	Improved word-list memory and recall	Significant improvement	No effect	Katada et al., 2014
Nicergoline	Alzheimer's	Improved GBS scale; improved MMS and SCAG scores	Significant improvement	Inconsistent - Increased at only one electrode site (Iwanami), not reported in Saletu study	Iwanami et al., 1993 Saletu et al., 1995
Scopolamine	Healthy volunteers	Worsened memory recognition task scores	Significant delay	Small/mixed effects	Potter et al., 2000

ERP P300 Data with Suggestive Correlation to Cognitive Changes







Modified from Thomas et al 2001

Electrophysiology as a Measure for Brain Function in Alzheimer's Disease

Sources of disruptions include:

- Neurotransmitter dysregulation
- Neuronal loss
- Synaptic loss/dysfunction
- Insufficient glucose and oxygen delivery
- Sleep deprivation

- Normal brain connectivity
- Normal cognition

Disrupted Network Communication

Disease onset

- Impaired brain connectivity
- Impaired cognition

ERP
P300 Latency

300 ms → **350 ms** → **400+ ms**

Athira Pharma Alzheimer’s Patient Data

ATH-1017 Treatment Improved P300 Latency in AD Subjects-CTAD 2019

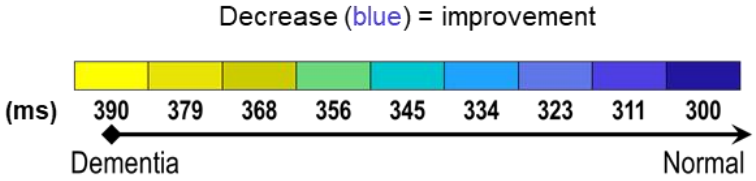
Phase 1b – AD Subjects

- **ATH-1017 – 40 mg**
- **(SC, OD, 8 days, n=7)**

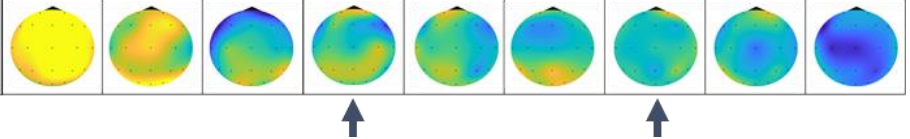
ERP OBSERVATIONS

ERP analysis to date suggests treatment effects on P300 latency

- Gradual decrease in latency over time in the treated group (n=7)



P300 Latency (ms)

Treatment	Day 1			Day 4			Day 8		
	Baseline	Hour 1	Hour 3	Pre-dose	Hour 1	Hour 3	Pre-dose	Hour 1	Hour 3
40 mg ATH-1017 (n=7)									

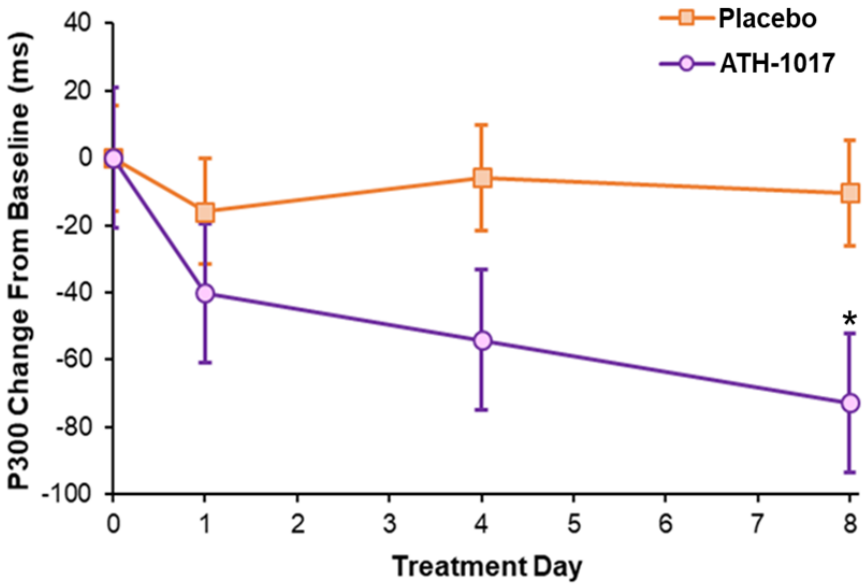
Decreased latency on pre-dose recordings (arrows) taken 24 hours after the last dose on the previous day, indicates sustained improvement

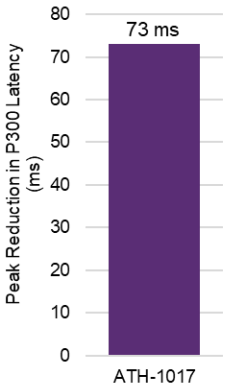
ATH-1017 Treatment Improved P300 Latency in AD Subjects-CTAD 2019

Phase 1b – AD Subjects

- Group averages of AD subjects receiving ATH-1017 (n=7) demonstrate decreased P300 over time
  - **Significant change from baseline observed on Day 8**
- AD subjects receiving placebo (n=4) had no consistent change from baseline to study end

P300 Latency: AD Subject ATH-1017 Treated and AD Subject Placebo





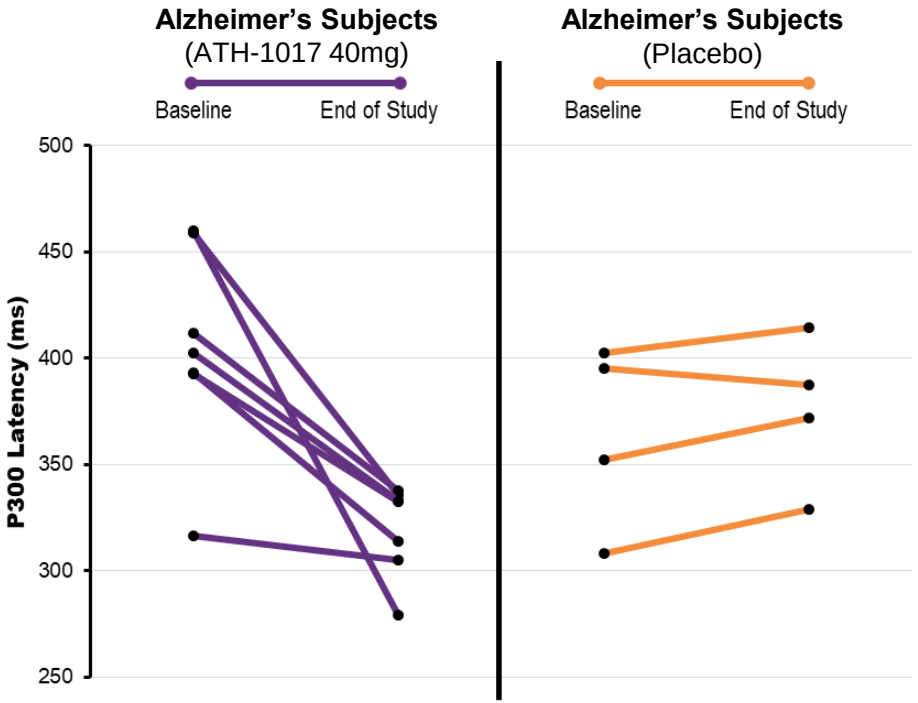
Note: P300 data from FZ, CZ, and PZ electrodes, Data plotted as mean +/- SE.. *p<0.05 with MMRM.

ATH-1017 Treatment Improved P300 Latency in AD Subjects-CTAD 2019

Phase 1b – AD Subjects

- Every AD subject receiving ATH-1017 had a level of improvement in P300 latency
- AD patients receiving placebo had no consistent response from baseline to end of study

P300 Latency: AD Subject ATH-1017 Treated and AD Subject Placebo



Note: P300 data from FZ, CZ, and PZ electrodes.

LIFT-AD and ACT-AD Trials

- Phase 2/3 –potentially pivotal
- Trial initiated Sept 2020
- Treatment for mild – moderate AD subjects
- Target enrollment of approximately up to 300 subjects
- Clinical endpoints (ADAS-Cog11 and ADCS-CGIC)
- Target data readout end of 2022

- Trial initiated Oct 2020
- Treatment for mild – moderate AD subjects
- Target enrollment of approximately up to 75 subjects
- P300 measure
- Clinical endpoints (ADAS-Cog11 and ADCS-CGIC)
- Target data readout early 2022

Learn more about both and find the nearest trial location at www.athiraclinicaltrials.com

Thank You

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