coined the term "mild cognitive impairment." In 1983 we published the Brief Cognitive Rating Scale (BCRS), consisting of measures derived from, and optimally concordant with the GDS stages. BCRS axes 1 to 5 describe changes in Concentration/Calculation ability, Recent Memory, Remote Memory, Orientation and Functioning, respectively. We now report changes in these BCRS measures in GDS stage 2/SCI persons over a 2 year mean interval, and corresponding affective changes. **Methods:** Otherwise healthy persons with SCI/GDS stage 2 from a previously published longitudinal study were selected with post baseline follow-up times of 1.5 to 3.0 years. The final cohort comprised 98 subjects. Subjects with significant affective symptomatology indicated by a baseline Hamilton Depression Scale (HDS) score $\geq$ 16, were excluded. Baseline characteristics included: age, 67.1 $\pm$ 8.8 years; educational background, 15.5 $\pm$ 2.6 years; Mini Mental Status Examination (MMSE) scores, 28.9 $\pm$ 1.2; and 64.3% were women. Mean follow-up time was 2.1 $\pm$ 0.3 years. The mean GDS stage changed significantly at follow-up to 2.16 $\pm$ 0.59 ($p<0.01$). Similarly, total scores on BCRS axes 1 to 5 worsened significantly at follow-up ($p<0.001$). **Results:** We now report that two individual BCRS axes, Remote Memory and Functioning, worsened significantly at follow-up (Wilcoxon p values 0.008 and 0.010, respectively). No significant changes were observed in the remaining 3 BCRS axes. Also, interestingly, 2 of the 21 items from the HDS, feelings of guilt and anxiety, improved significantly at follow-up. **Conclusions:** The BCRS measures in this study have been used as part of a primary outcome assessment in US, EU and worldwide approvals of current AD medications (e.g., rivastigmine and memantine). These same measures collectively, are sensitive to change in persons with subjective decline only, over a 2 year interval. Also, SCI persons appeared to become less "guilt ridden" and anxious over this interval.

F1-04-03 THE ALZHEIMER'S PREVENTION INITIATIVE'S (API'S) EVOLVING PERSPECTIVE ON OUTCOMES IN PRECLINICAL TRIALS

Pierre N. Tariot, *Banner Alzheimer's Institute, Phoenix, AZ, USA. Contact e-mail: Pierre.tariot@bannerhealth.com*

Background: The choice of outcomes for clinical trials in preclinical AD is influenced by factors such as trial goals (e.g., proof-of-concept, target engagement, demonstrating efficacy), participant characteristics, type of intervention, available infrastructure, data available to assess potential performance, Health Authority input). API and its partners have confronted these issues in conceiving and implementing its two active trials. **Methods:** API first proposed preclinical trials in cognitively unimpaired *PSEN1 E280A*mutation carriers and APOE4 homozygotes using biomarker outcomes to make go-no-go decisions. Based on input from prospective industry partners and Health Authorities, the focus was broadened to include clinical outcomes. We used existing prospective datasets to empirically derive a composite cognitive test score as a primary endpoint to track change in the ADAD trial, serving as a single measure of multiple cognitive domains, reducing the risk of Type 1 error. The primary aim of the API APOE4 homozygote clinical trial is to assess time to MCI or dementia due to AD and/or change in a different composite cognitive test score defined specifically for this trial. External to this trial, efforts will be undertaken to validate the clinical meaningfulness of change in the composite test scores. In both trials, key secondary clinical outcomes were selected, and biomarker aims were modified to address possible prognostic, predictive and theragnostic utility. **Results:** The sample size for the API Colombia trial, conducted with the Neurosciences Group of Antioquia and Genentech/Roche, is 200 carriers and, to maintain genotype blind, 100 noncarriers; that for the 4-arm APOE4 homozygote trial, conducted in partnership with Novartis/Amgen, is approximately 1340. Sample size estimates will be provided for biomarker outcomes. **Conclusions:** In order to receive Health Authority approval, experimental therapies in preclinical trials are required to show a clinical effect. There is no consensus regarding the optimal approaches to do so. API and its partners are testing assumptions and refining methods, and are addressing the future potential for biomarker outcomes to serve as "reasonably likely" therapeutic surrogates for decision-making in drug development. We hope these findings, which will be shared, will help advance the field's efforts to find ways to assess clinically meaningful change in preclinical trials.

F1-04-04 ADVANCING CLINICAL TRIALS USING REAL-TIME, ECOLOGICALLY VALID DATA CAPTURE METHODOLOGY

Jeff A. Kaye[1,2,3], Judith Kornfeld[3], **Hiroko H. Dodge[1,2,3,4]**, *[1]Oregon Health & Science University, Portland, OR, USA; [2]NIA-Layton Aging & Alzheimer's Disease Center, Portland, OR, USA; [3]Oregon Center for Aging & Technology (ORCATECH), Portland, OR, USA; [4]University of Michigan, Ann Arbor, MI, USA. Contact e-mail: hdodge@med.umich.edu*

Background: Detecting meaningful change in clinical trials at early stages of drug development or for dementia prevention therapies is challenged by the insensitivity and variability of current measures. Changes in data capture methodology taking advantage of continuous home-based measurements of function using simple embedded sensors and devices provides an opportunity to improve the sensitivity and ecological validity of trials. Based on this principle a research platform (at The Oregon Center for Aging and Technology; ORCATECH) has been developed that employs pervasive computing technologies to harvest life's data in real time and show how using these data with high-frequency metrics that are reflective of tangible function may improve the conduct of trials. **Methods:** A total of 265 participants were enrolled beginning in 2007 in the Intelligent Systems for Assessing Aging Changes Study (ISAAC). Continuous data from subjects followed over 4 years are used as an example of this approach to show that these data allow us to collect enough data points to generate *individual-specific distributions* of functional outcomes such as computer usage and walking speed/variability within a short duration (e.g., 3 months). Using generalized mixed effects model, we estimated sample size needed to detect clinically meaningful reduction in longitudinal declines in functional outcomes. **Results:** Sample sizes (or trial durations) required to achieve sufficient power to detect desired trial effects are significantly reduced using this approach in comparison with traditional clinical trial designs. For example, sample size estimates indicated approximately 2000 subjects with a follow-up duration of 4 years would be needed to achieve a 30% effect size when the outcome is

an annually assessed memory test score. Using the metrics derived from our study, the required sample size can be reduced to lower than 100. **Conclusions:** Using individual-specific thresholds obtained from high-frequency in-home monitoring data that is focused on ecologically valid patient function provides an efficient alternative methodological trial paradigm. Future studies applying this method to various trial outcomes are warranted to validate the generalizability of this approach in clinical trials.

SUNDAY, JULY 24, 2016
PLENARY SESSION
PL-01

PL-01-01 PRECLINICAL TO CLINICAL TRANSLATION FOR TAU THERAPEUTICS

David M. Holtzman, *Washington University School of Medicine, St. Louis, MO, USA; Hope Center for Neurological Disorders, Saint Louis, MO, USA; Knight Alzheimer's Disease Research Center, St. Louis, MO, USA. Contact e-mail: holtzman@neuro.wustl.edu*

Abstract not available.

SUNDAY, JULY 24, 2016
ORAL SESSIONS
O1-01
NEUROIMAGING: FACTORS RELATING TO BRAIN MAINTENANCE

O1-01-01 ACTIVE AND PASSIVE RESERVE DIFFERENTIALLY MITIGATE COGNITIVE SYMPTOMS IN DEMENTED AND NON-DEMENTED STAGES OF ALZHEIMER'S DISEASE

Colin Groot[1], Anita C. van Loenhoud[2], Bart N. M. van Berckel[2,3], Frederik Barkhof[3,4], Teddy Koene[2,3], Charlotte E. Teunissen[2,3], Philip Scheltens[2,3], Wiesje M. van der Flier[2,3], Rik Ossenkoppele[2,3,5], *[1]Department of Radiology & Nuclear Medicine, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, Netherlands; [2]VU University Medical Center, Amsterdam, Netherlands; [3]Neuroscience Campus Amsterdam, Amsterdam, Netherlands; [4]Department of Radiology and Nuclear Medicine, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, Netherlands; [5]VU University Amsterdam, Amsterdam, Netherlands. Contact e-mail: c.groot3@vumc.nl*

Background: Inconsistencies in the degree of Alzheimer's disease (AD) neuropathology and subsequent cognitive impairment may be explained by mediating effects of active and passive forms of cognitive reserve. In the present study, we examined the relationship between active/passive cognitive reserve and neuropsychological functioning in patients in the non-demented and demented stages of AD. **Methods:** Our sample included 650 patients with positive amyloid-beta biomarkers (PET or CSF) for AD and a clinical diagnosis of subjective cognitive decline (SCD, n=69), mild cognitive impairment (MCI, n=130) or AD dementia (n=451, Table 1), who underwent a neuropsychological test battery including memory, attention, language, executive functioning and visuo-spatial cognitive domains. T1-weighted MR images (performed on 3T-scanners) were segmented using statistical parametric mapping (SPM12). ICV, a proxy of passive reserve, was calculated by summing gray matter, white matter and cerebrospinal fluid volumes. Education, a proxy of active reserve, was obtained using a standardized scale (Verhage, range: 1-7). Brain atrophy was operationalized by corrected whole-brain gray matter volumes. Multiple linear regression models, corrected for brain atrophy, age, sex and scanner type, were used to examine independent predictive effects of education and ICV on neuropsychological function. To control for multicollinearity, education, ICV and brain atrophy parameters were centered before being included as predictors. **Results:** Stratifying the sample into patients with (n=451) and without (i.e. SCD and MCI, n=199) dementia, we found positive effects for education on attention, executive functioning and language domains in patients without dementia, and on attention, executive functioning and visuo-spatial domains in the dementia group. Furthermore, ICV showed a positive relation to executive functioning in patients without dementia, while it showed a positive effect on attention, executive functioning

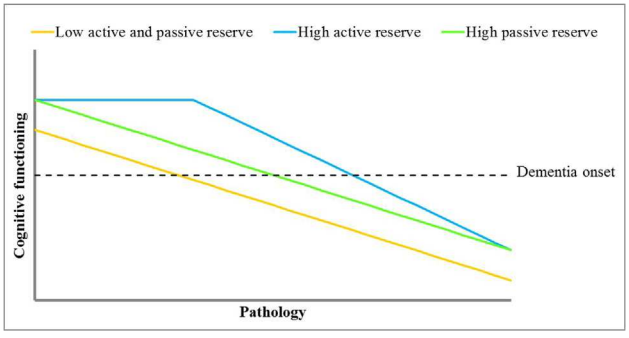

Table 1
Demographic and clinical characteristics

	Patients without dementia	Patients with dementia	P-value
N	199	451	
Diagnosis	SCD (69) MCI (130)	AD dementia (451)	
Sex (female/male)	93/106	239/212	.14
Age	66.6 (7.5)	66.1 (7.4)	.39
Education (median (range)	5 (2-7)	5 (2-7)	< .01
ICV	1.52 (.15)	1.50 (.16)	.18
Brain atrophy[a]	.41 (.04)	.38 (.04)	< .01
MMSE	27.0 (2.2)	20.6 (4.4)	< .01
Cognitive function z-scores[b]			
Memory	-1.39 (1.57)	-4.91 (3.33)	< .01
Attention	-.38 (.81)	-2.50 (2.67)	< .01
Executive functioning	-.50 (.91)	-2.44 (1.79)	< .01
Language	-.29 (.58)	-1.49 (1.49)	< .01
Visuo-spatial	-.21 (.86)	-2.37 (2.95)	< .01

Values are depicted as mean (standard deviation), unless otherwise indicated. ICV- intracranial volume in dm3, MMSE - Mini-Mental State Examination, SCD - Subjective cognitive decline, MCI - mild cognitive impairment.

[a]corrected gray matter volume, lower score is indicative of more atrophy.

[b]calculated with mean and standard deviation of independent healthy control group.