









האוניברסיטה העברית ביהושלים
THE HEBREW UNIVERSITY OF JERUSALEM

The probabilistic approach to Alzheimer's disease

Neuropsychiatry Lab

What is AD? Timeline of AD clinical criteria

	NINDS (1984) 	IWG – I (2007) 	NINDS (2011) 	IWG – II (2014) 	NIA - 2018 	IWG - 2021 
Dementia	MMSE	-	MMSE	-	-	-
Cognition	2/8 <i>(see next slide)</i>	Episodic memory	Memory + 1/3 <i>(see next slide)</i>	Typical AD: memory Atypical AD: 1/3	-	Specific phenotypes
Biology	-	PET/ Tau/ Presenilin	“May increase certainty”	PET/Tau+Aβ / Presenilin	ATN	Positive biomarkers



PERSPECTIVES

The probabilistic model of Alzheimer disease: the amyloid hypothesis revised

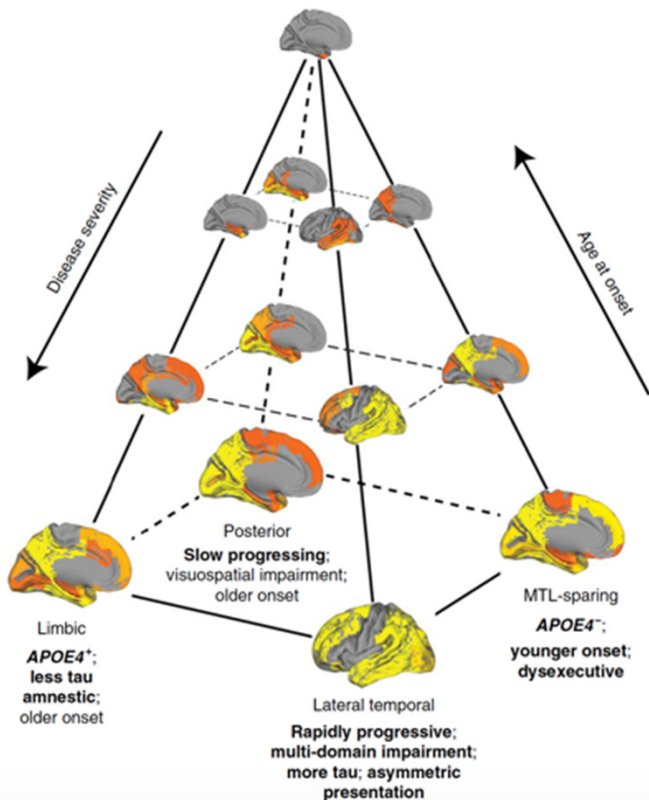
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downstream events that finally lead to cognitive impairment and dementia^{4,5}.

It has been the dominant model of AD pathogenesis for more than 30 years and the guiding influence for drug development, which to a large degree has aimed to produce compounds that either reduce A β production (secretase inhibitors) or increase A β clearance (immunotherapies). The hypothesis implicitly assumes a deterministic cause–effect model (that is, a chain of events that will invariably produce the same output from a given

The probabilistic approach to AD

Phenotype



Vogel et al., Nature Medicine 2021

MRFs

Table 2 Predictors of MCI in the clinical risk model based on basic demographic and medical history features^a

Variable	HR (95% CI) ^b	Risk score contribution
Men and women		
Education ≤12 y	1.50 (1.24-1.83)	2
Self-reported memory concerns	1.41 (1.15-1.73)	2
Ever diagnosed with alcohol problem	1.70 (1.09-2.65)	3
History of stroke	1.26 (0.94-1.70)	1
Diabetes and age at assessment <75 y	2.21 (1.27-3.84)	5
Diabetes and age at assessment 75-84 y	1.35 (0.97-1.87)	2
History of atrial fibrillation	1.20 (0.93-1.53)	1
Predictors for women only		
Current smoker	1.83 (0.93-3.60)	3
Midlife dyslipidemia	1.34 (0.96-1.87)	2
Definite or probable diabetes in midlife	1.34 (0.67-2.69)	2
Midlife hypertension	1.27 (0.94-1.72)	1

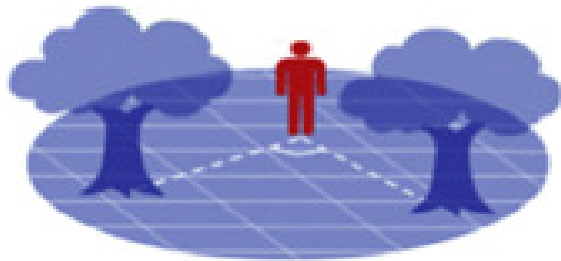
Pankratz et al., Neurology, 2015

Objectives

- Diagnose early (in scale) through personalized orientation testing
- Identify personalized modifiable risk factors (in scale)

Definition: orientation

Orientation: “Tuning between the subject and the internal representation he forms of the corresponding public reference system; the external world” (Berrios, 1982; Peer et al 2015)



SPACE

Map (space, continuum)



TIME

Mental (time) line



PERSON

Cognitive graph of social network

For review see Coughlan et al., 2018; Arzy and Schacter 2019; also works by the Spiers and Axmacher labs

Mental and Standard Orientation

Which is closer?

(Geographically)

Jerusalem Tel-Aviv

(Chronologically)

Retirement Son's
wedding

(Personally)

Son-in-Law Boss

What is the

- Year
- Month
- Date
- Day
- Season

Where are you

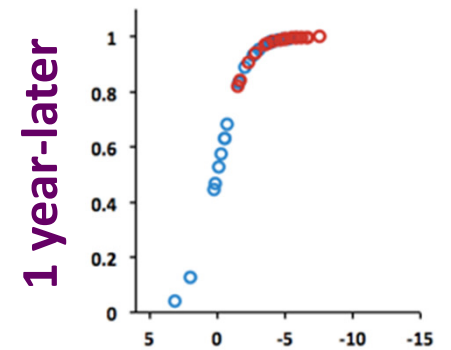
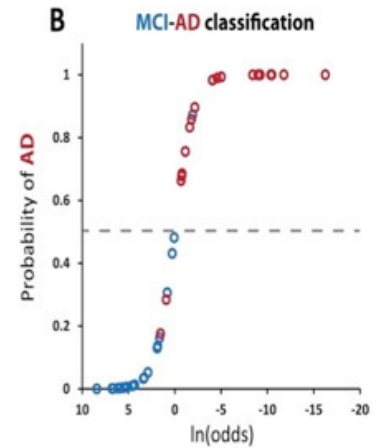
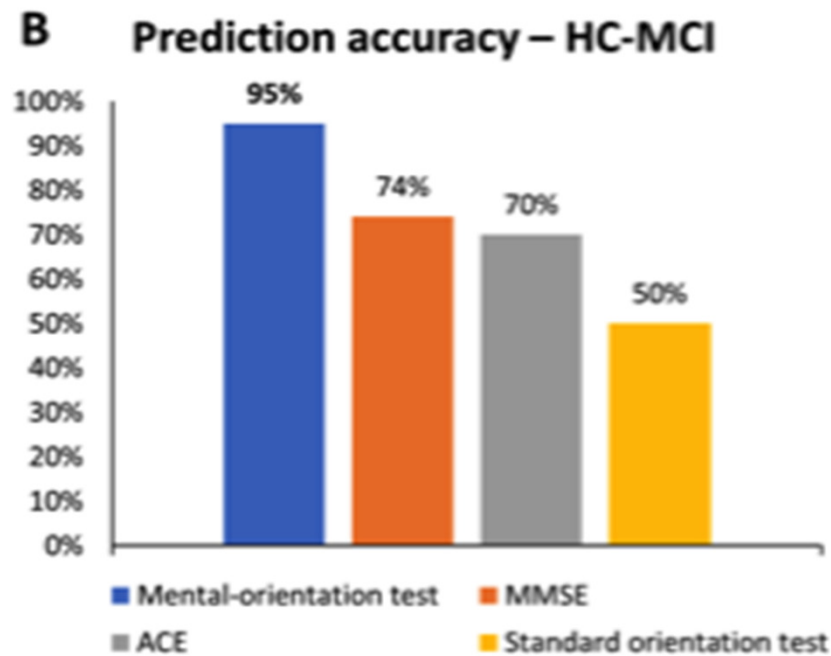
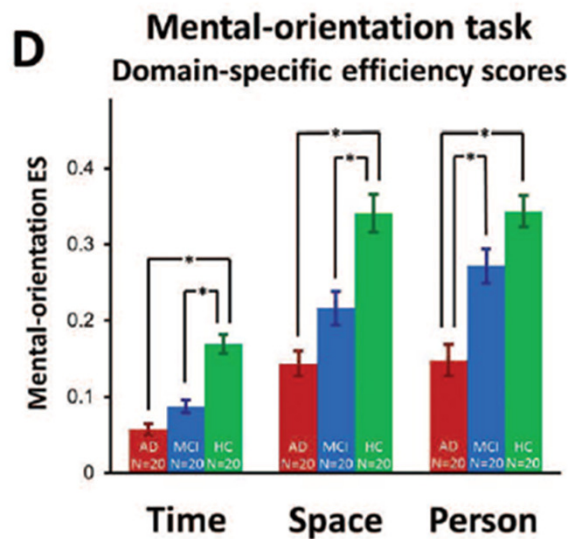
- Country
- Region
- City
- Hospital
- Floor

To test orientation independently from memory only personally familiar and correctly localized places, event and people were used

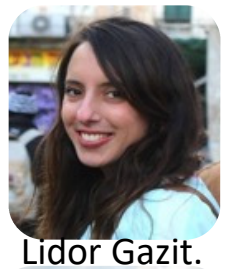
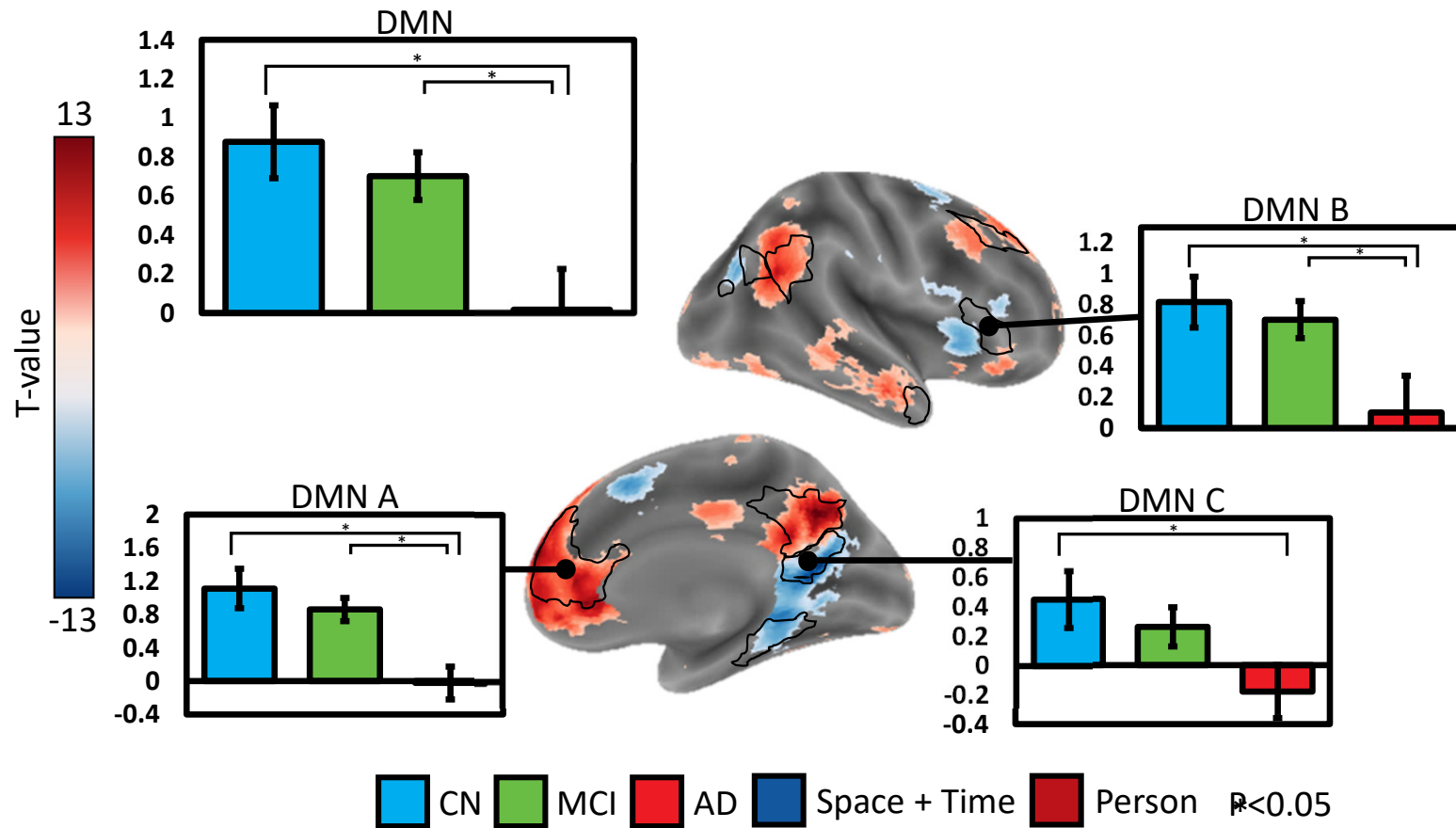
Peer et. al, 2015; Peters-Founshtein et. al, 2018; Dafni-Marom et. al, 2019

Orientation along the AD continuum

Orientation is able to distinguish between CN, MCI and AD



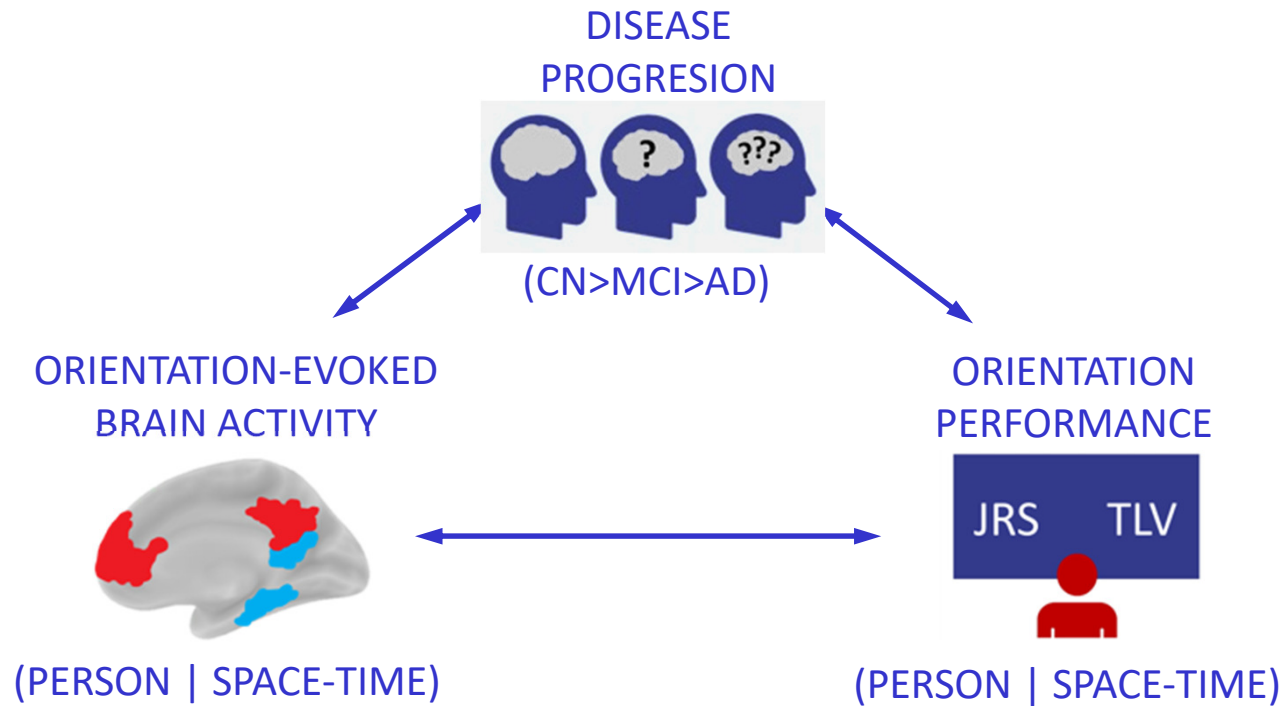
PET-fMRI Orientation task along the AD continuum (n=60)



Greg Peters-Founshtein

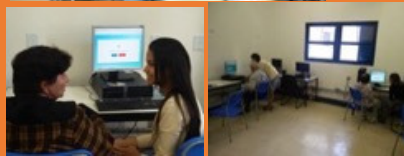
Peters-Founshtein, Gazit et al., in prep; Dafni-Merom et al., Ann Clin Trans Neurol, 2019

Interim Conclusions

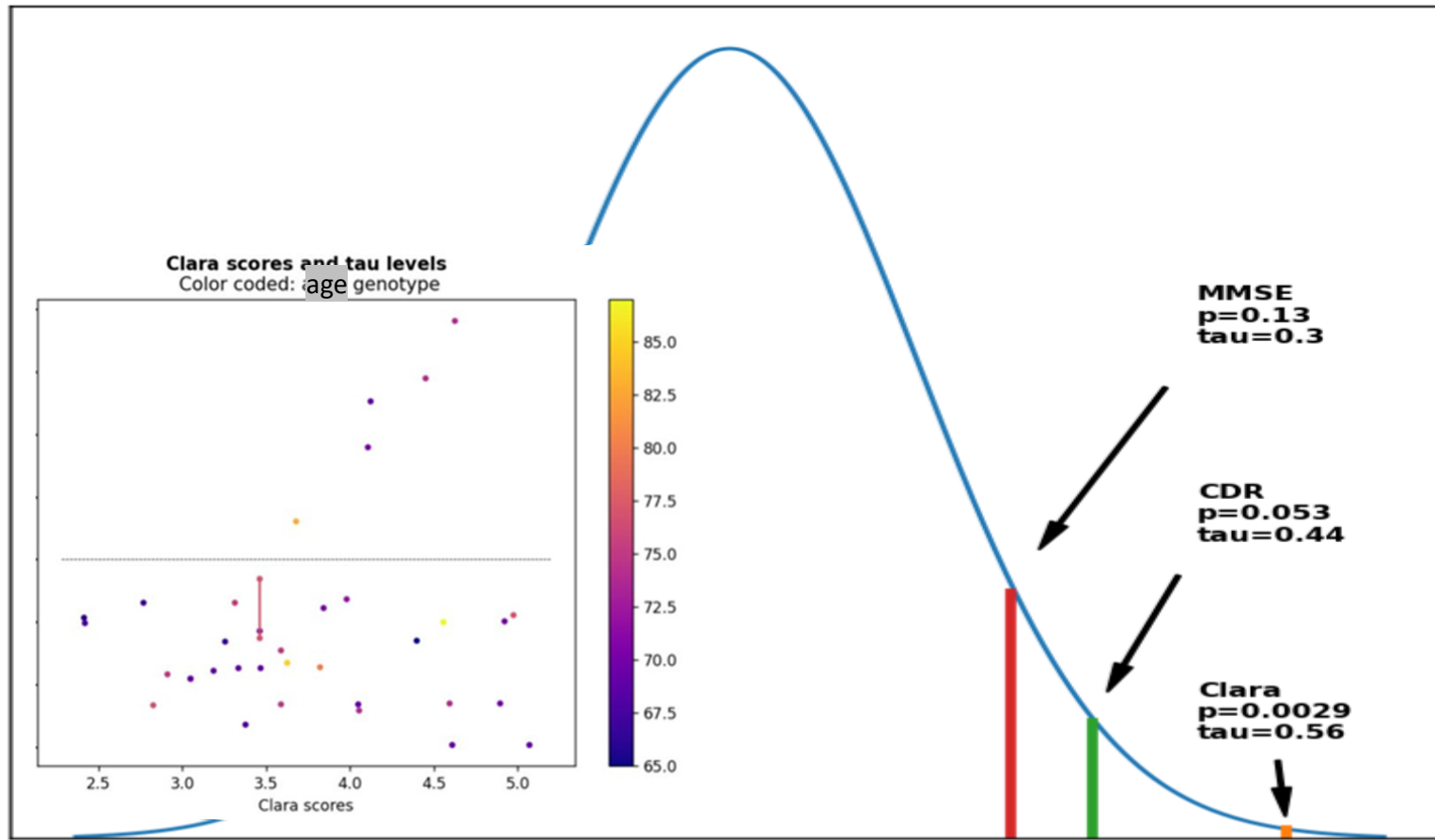


Disorientation is a sensitive marker of AD because orientation-evoked activity “obeys” AD-related neuropathology

CLARA AROUND THE WORLD

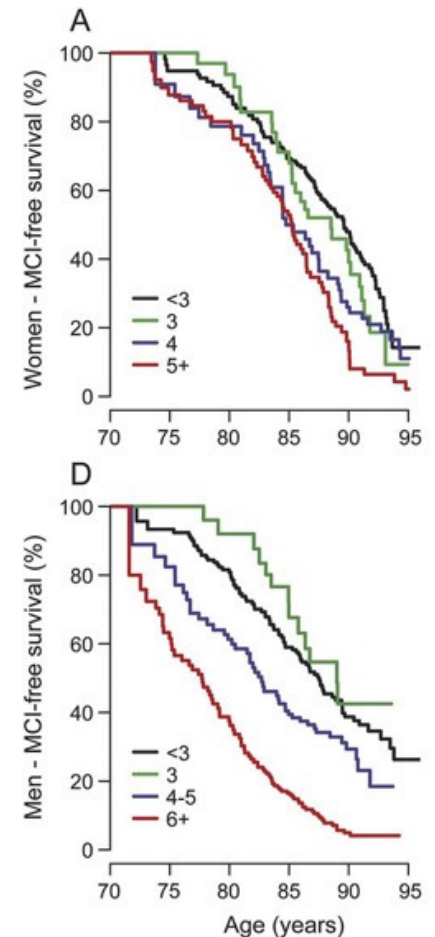


Clara consistency : Kendall tau and probability values for clara scores in two time points with a near 1 year difference



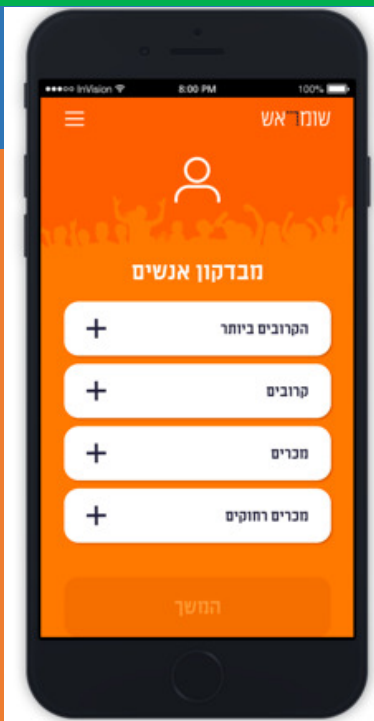
Personalized MRFs

- Application of cox proportional hazard function on large scale data
- Personalization through “orientation signature”

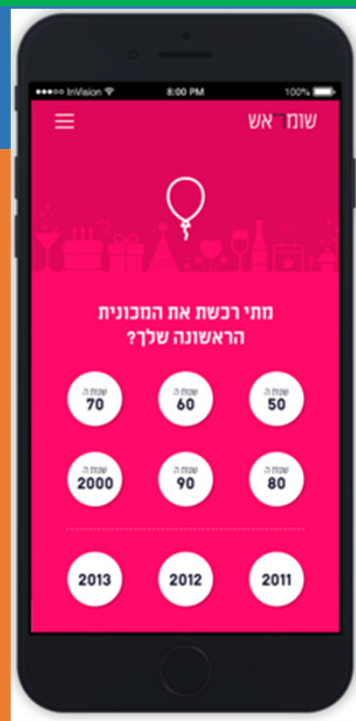


Kaplan–Meier curves for MCI-free survival among participants in the Mayo Clinic Study, classified by quartiles of the cross-validated MCI risk scores measured at baseline (Pankratz et al., 2015)

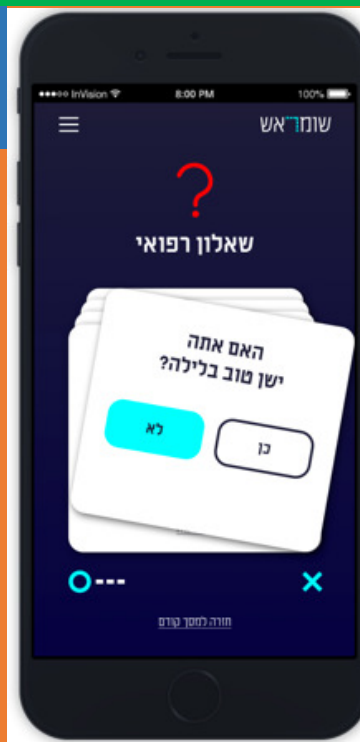
Clara 2.0



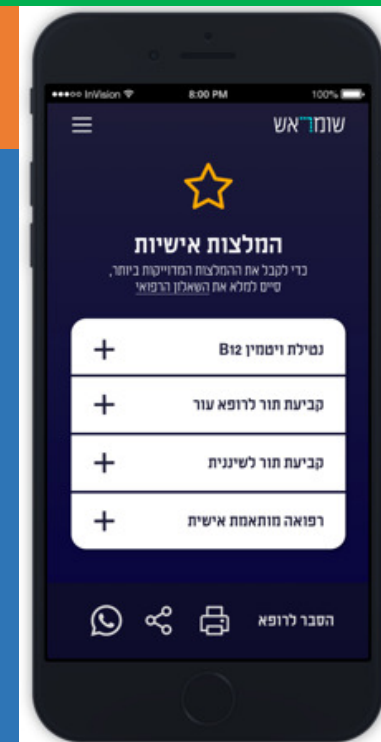
PEOPLE



EVENTS



EHR



RECOMMENDATIONS

Conclusions

- **Disorientation is a major AD phenotype**
- **Disorientation maybe diagnosed early through Clara**
- **As in classical medicine, AD is a multifactorial disorder**
- **Treatment of such factors should keep AD below the threshold**