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# Digital cognitive markers for Alzheimer's disease

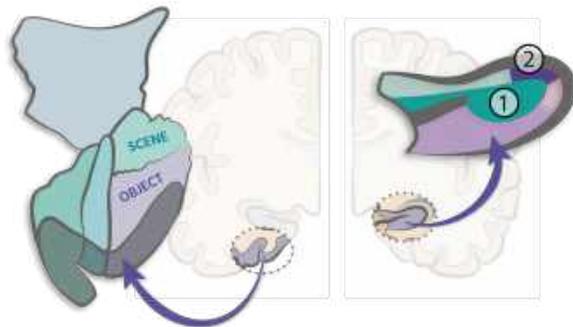
Closing critical gaps in research, clinical trials and healthcare

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## What is unique about neotiv cognitive markers?

- > Anatomically specific with a unique concept
- > Proven sensitivity to clinical and biomarker status
- > Proven utility in unsupervised and supervised settings
- > High-frequency tracking of cognitive trajectories and unique validation for cognitive decline



anatomically specific tests



neotiv digital platform



## Why can neotiv tests be considered cognitive markers in Alzheimer's disease?

Correlation with early tau burden (CSF and PET validation) in preclinical Alzheimer's disease



Outcome measure in preclinical drug trials

High accuracy to identify biomarker positive (A $\beta$ 42+/p-tau+) individuals among persons with cognitive complaints (subjective cognitive decline and mild cognitive impairment)



Case-finding (biomarker positive decliners) and monitoring in healthcare and drug trials

Proven population-level reach (in Citizen Science project)



Enables pre-healthcare case finding



# What is the unique concept behind neotiv tests?

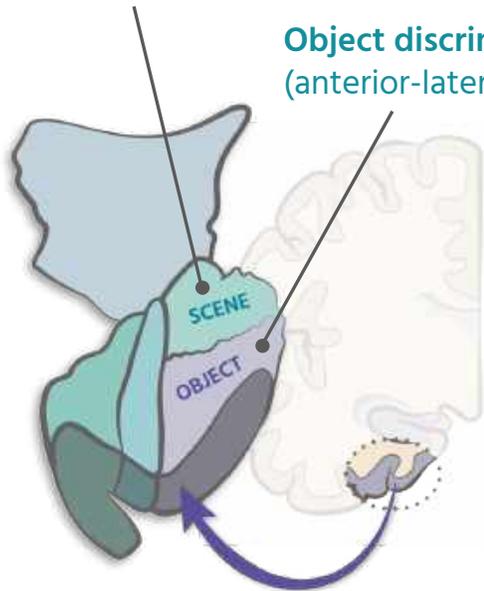
Targeting specific disease onset regions // **ZOOM-IN**



Targeting widespread disease networks // **ZOOM-OUT**

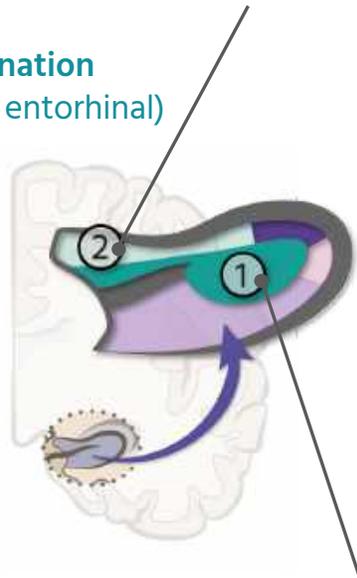
**Scene discrimination**  
(posterior-medial entorhinal)

**Object discrimination**  
(anterior-lateral entorhinal)



**Medial temporal lobe regions**

**Pattern completion**



**Pattern separation**

**Hippocampal subfields**

Real-life like stimulus material  
(secured neotiv-IP)

**Frontal**

- Adaptation of TMT A/B
- Adaptation of Digit symbol test

**Parietal and midline parietal**

- Complex scene recognition
- Scene discrimination

**Temporal**

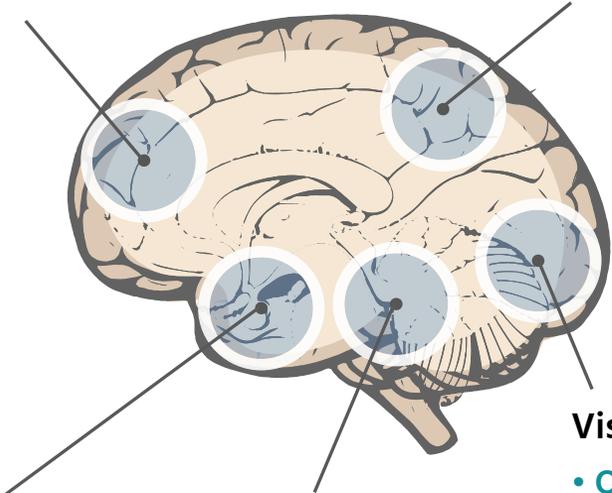
- Complex scene recognition

**Interior temporal**

- Face-name association
- Scene discrimination

**Visual**

- Object discrimination



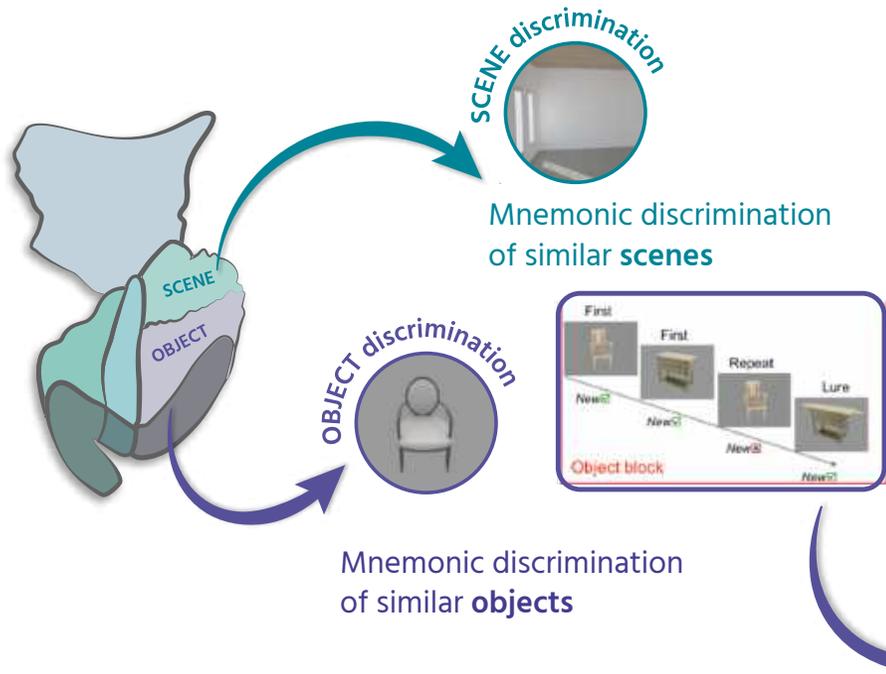
Caption: **Brain region** Established neuropsychological assessments

**neotiv cognitive tests**



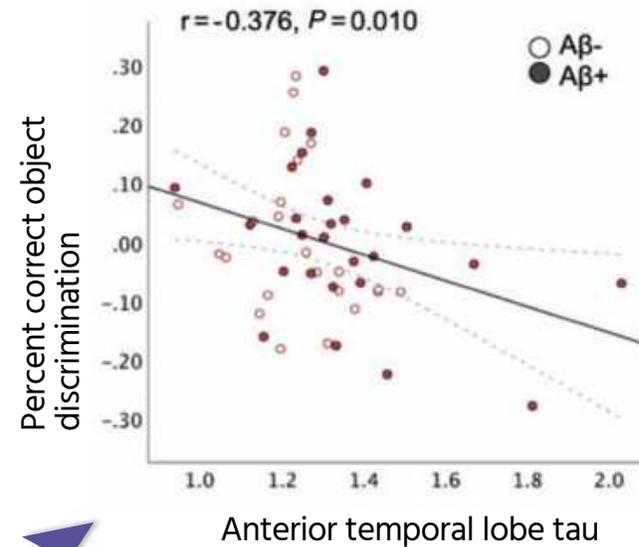
# Insights into validation – zooming-in on the entorhinal cortex

Tests specific for entorhinal pathways developed in fMRI studies

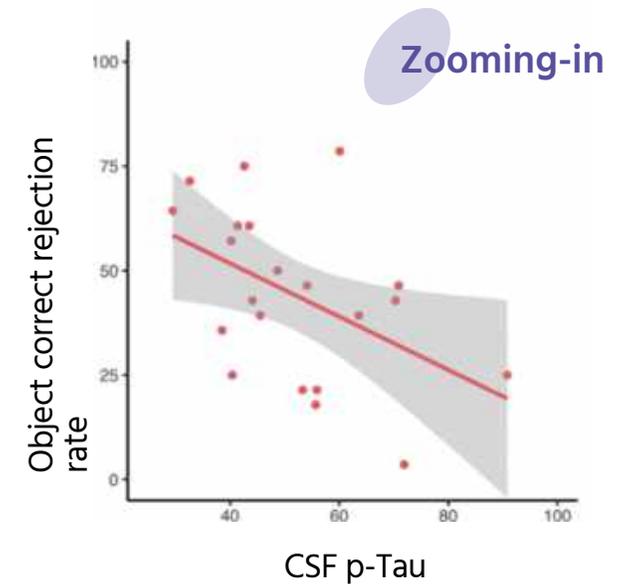


Berron et al., NBA, 2018; Berron et al., J Neurosci., 2019; Maass et al., elife, 2015

Biomarker correlated – Object (but not scene) mnemonic discrimination (specific to anterior-lateral entorhinal cortex) is related to preclinical tau-pathology as measured with PET and CSF



Maass et al, Brain 2019; Similar results also with CSF: Berron et al, J Neurosci, 2019

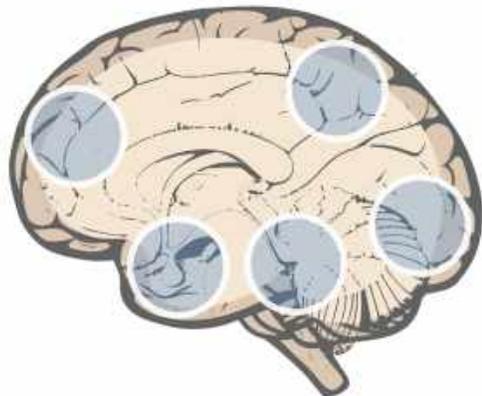




# Insights into validation – zooming-out to widespread disease networks

Test specific for the episodic memory network developed in fMRI studies

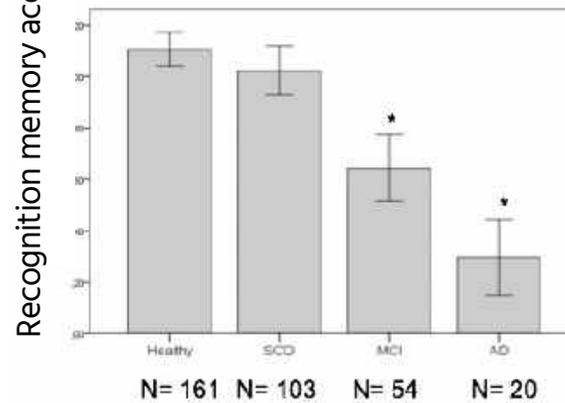
Widespread network comprising midline parietal and temporal lobe



Recognition memory for complex scenes

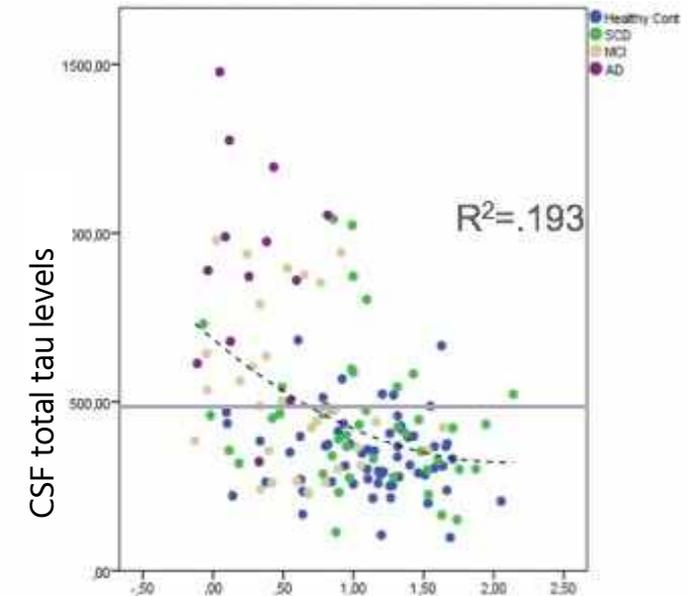
- Biomarker correlated – Recognition memory accuracy related to CSF tau levels in preclinical and prodromal AD.
- Memorability of specific images related to diagnostic accuracy (AI-based) of mild cognitive impairment

Recognition memory accuracy



Identification of MCI participants

Zooming-out



Recognition memory accuracy Correlation to CSF tau pathology

Unpublished data.; Düzel et al. Alz & Dem DADM 2018; Bainbridge et al., Alz & Dem DADM, 2019

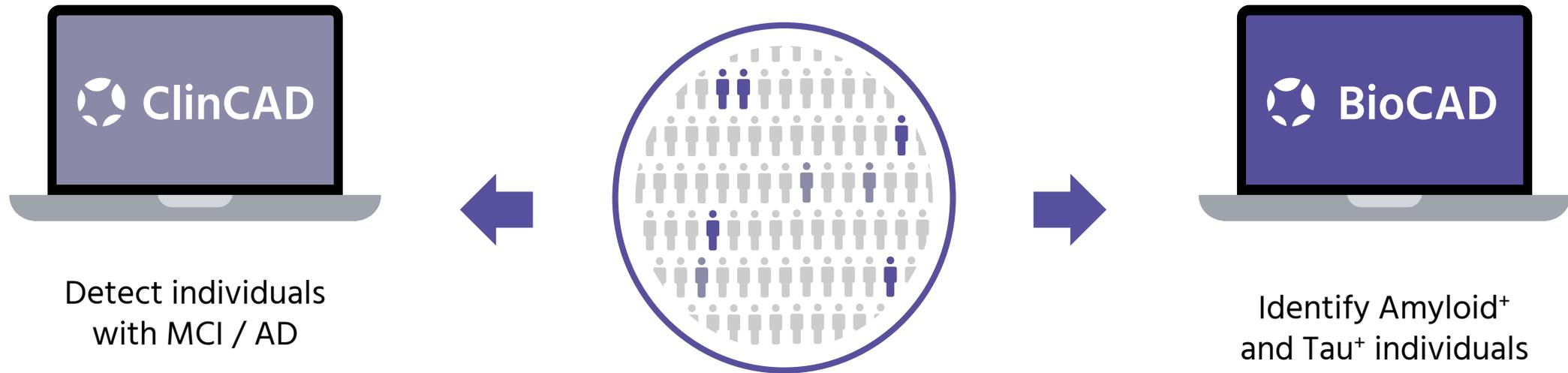


## All available neotiv tests

neotiv cognitive test	Anatomical region	Cognitive mechanism	Cognitive domains
<b>Object mnemonic discrimination</b>	Perirhinal, anterior-lateral entorhinal / transentorhinal, dentate gyrus, amygdala	Pattern separation, object processing, perceptual discrimination	Episodic memory, working memory, perception
<b>Scene mnemonic discrimination</b>	Parahippocampal, posterior-medial entorhinal, dentate gyrus, midline parietal	Pattern separation, perceptual discrimination, spatial processing, scene boundary processing	Episodic memory, working memory, perception
<b>Complex scene recognition</b>	Hippocampus, ento-/ perirhinal, parahippocampal, precuneus, parietal	Recognition, recollection, familiarity	Episodic memory, familiarity
<b>Scene-object pattern-completion</b>	CA3, CA1, perirhinal, parahippocampal, precuneus	Pattern completion, associative memory, recollection	Episodic memory, consolidation
<b>Face-name association</b>	Fusiform, lateral-temporal	Associative memory, face perception, language	Episodic memory, memory association, face perception
<b>Adapted trail making test A/B</b>	Frontal, parietal	Sustained attention, cognitive flexibility	Attention, executive functions
<b>Adapted digit symbol substitution</b>	Frontal, parietal	Associative binding, task switching, flexibility, maintenance, memory	Attention, executive functions, working memory



We combine neotiv cognitive tests into neotiv cognitive composite scores for optimal clinical- and biomarker-based identification

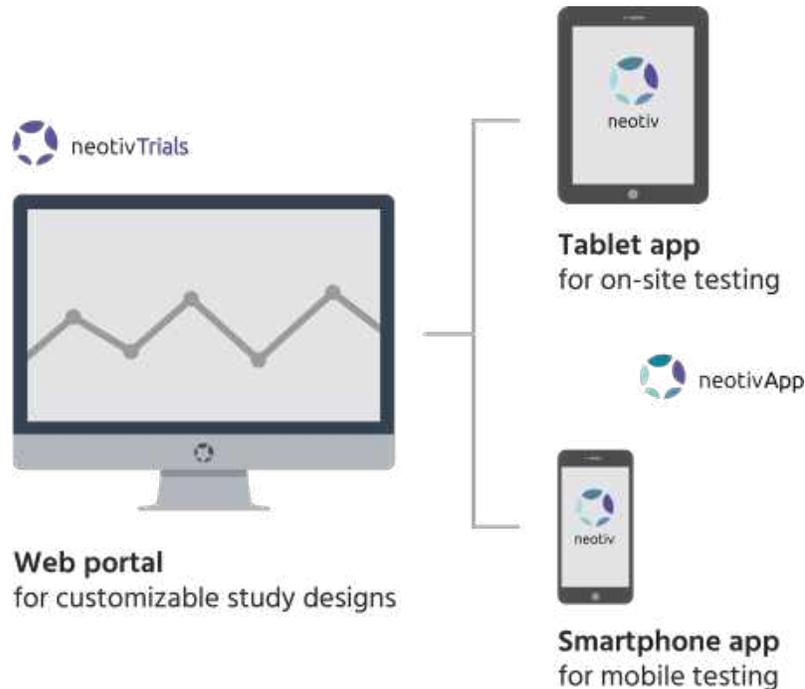


- ▶ Further information about our validation results, sensitivity, specificity and the relationship with other cognitive tests is available in our validation package (under NDA)



## The technology behind neotiv – more than an app

### Digital platform for customizing cognitive testing for any type of study/trial design



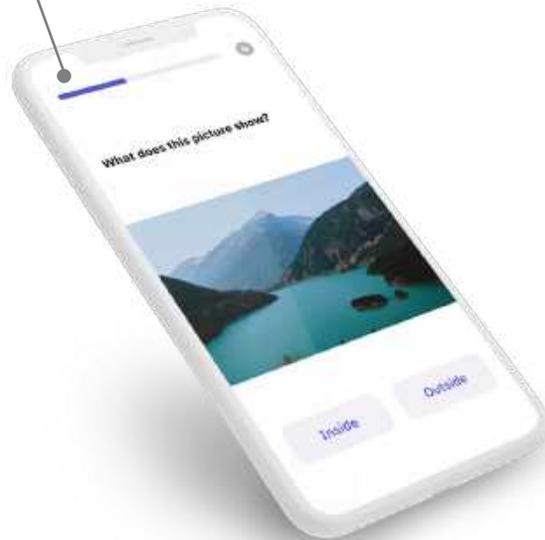
### Customize study design as a sponsor, CRO or investigator

- Use the white labeling options
- Set time schedule of specific cognitive tests and their reminders and adapt to individual needs if necessary
- Select the neotiv cognitive tests you need for your study
- Add questionnaires (i.e. mood, sleep, side effects etc.) and integrate them into the test schedule as you need
- Add companion/advisory content for participants
- Create encrypted login codes and send them to specific participants
- Track the progress of your participants in real time
- Access data for clearly defined purposes at any time and export data as CSV anytime



## neotiv App tests for on-site and mobile testing

### Complex scene recognition



### Pattern completion



### Pattern separation

- Scene discrimination
- Object discrimination



### Established neuropsychological assessments

- Trials A/B
- Digits and Symbols

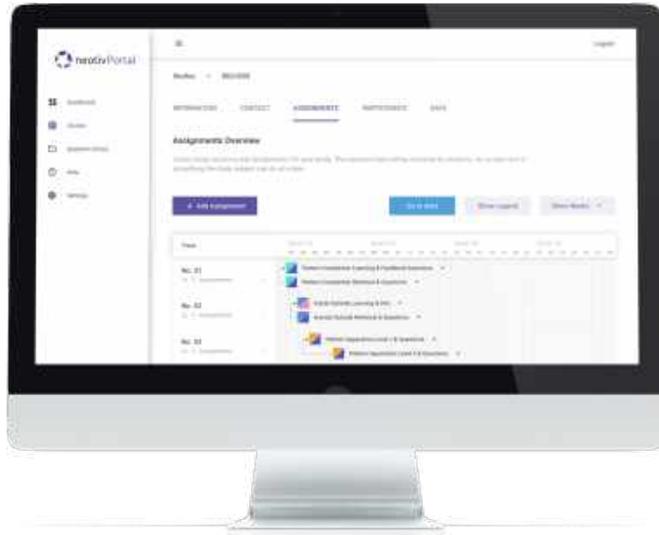


- IP protected neotiv cognitive tests and adapted established neuropsychological assessments
- Usability is the key to the neotiv App design
  - > Tested i.e. in Citizen Science campaign (+3000 users)
  - > Real-life like stimulus material (secured neotiv IP)

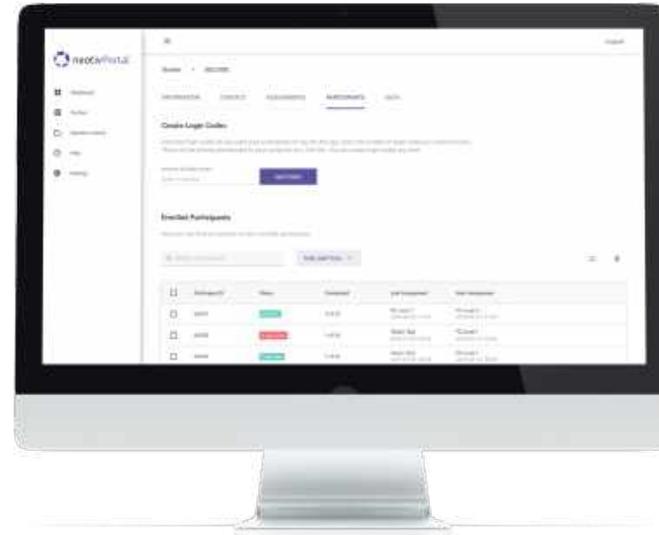


## Web portal for customizable study designs

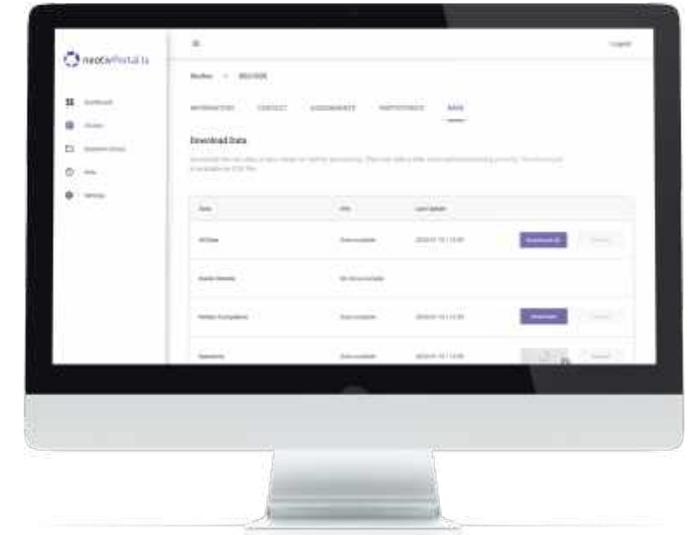
Show assignments overview



Monitor enrolled participants

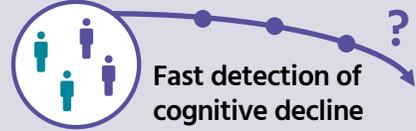
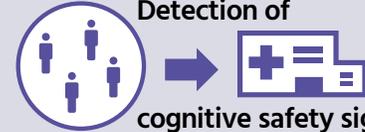


Export data





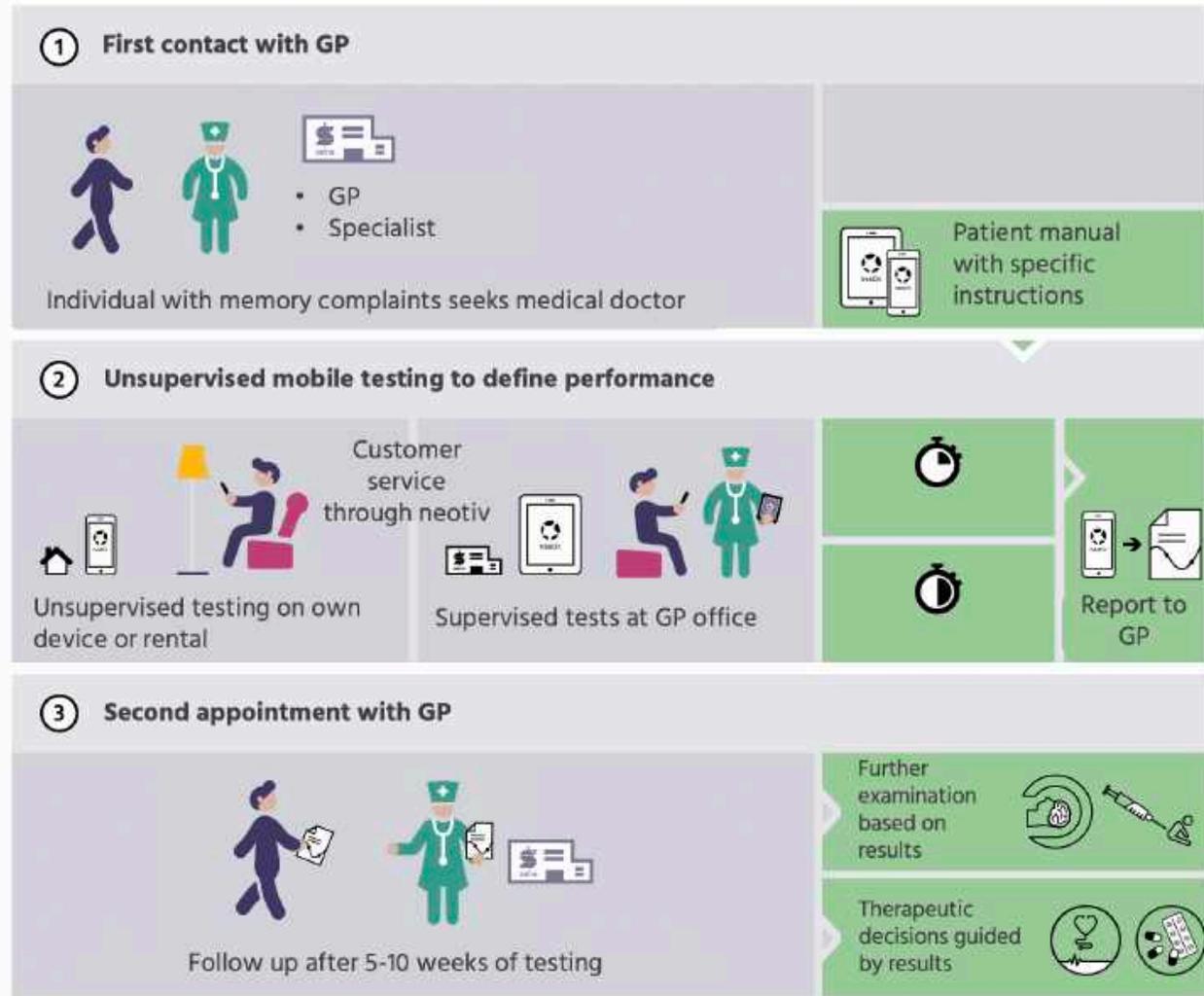
# You can address key challenges of cognitive assessment in Alzheimer's disease research and trials with neotiv

Challenges	neotiv's solutions	In short
<p><b>Population-level reach of cognitive testing needed for efficient recruitment</b></p>	<ul style="list-style-type: none"> <li>• Highly versatile, easy to disseminate, scalable digital technology</li> <li>• Innovative cognitive tests sensitive to clinical diagnosis and biomarker status</li> </ul>	 <p>Population-level reach</p>
<p><b>Takes years to identify and recruit those with declining cognition</b></p>	<ul style="list-style-type: none"> <li>• neotiv's high-frequency monitoring for fast detection of cognitive decliners</li> <li>• Minimized practice effects through more than 20 parallel versions</li> </ul>	 <p>Fast detection of cognitive decline</p>
<p><b>Ceiling and floor effects due to wide cognitive range of cognitive impairment</b></p>	<ul style="list-style-type: none"> <li>• neotiv cognitive tests can cover a wide-range of stages due to lack of ceiling and floor effects</li> </ul>	 <p>Covers a wide-range of stages</p>
<p><b>Small effect size of treatment in preclinical stage (anatomically confined benefit)</b></p>	<ul style="list-style-type: none"> <li>• Anatomically zoomed tests for detecting effects of early disease modification and specific symptomatic treatments</li> <li>• Trajectory tracking with high-frequency monitoring</li> </ul>	 <p>Treated group Untreated group</p>
<p><b>Safety signals for cognitive worsening in a trial difficult to obtain</b></p>	<ul style="list-style-type: none"> <li>• neotiv's high-frequency monitoring for rapid detection of cognitive safety signals</li> </ul>	 <p>Detection of cognitive safety signals</p>

**Caption:**  Healthy (cognitively normal)  Subjective memory complaints  Preclinical Alzheimer (biomarker positive)  Prodromal Alzheimer (MCI, biomarker positive)  Cognitive trajectory (detected with HF-monitoring)



# You can use neotiv to assist diagnostic assessment in healthcare



## Patient journey of individuals with memory complaints

- Patient journey developed in collaboration with GPs and dementia specialists, supported by the German Center for Neurodegenerative Diseases (DZNE)
- Extensive documentation and materials for healthcare professionals and patients provided by neotiv
- Customer service for patients provided by neotiv

Pharmacological interventions can be supported by using the app as **drug companion**

Inclusion in studies can easily be implemented based on patient journey

Biomarker profile and cognitive performance as outcome



## neotiv tests and composite scores in the Alzheimer's disease continuum close critical gaps in research, drug trials and health care

- > neotiv has developed and composed a unique suite of innovative cognitive tests
- > Very good correlation with early (preclinical) tau burden
- > High accuracy to identify biomarker positive (A $\beta$ 42+/ptau+) individuals among individuals with memory complaints
- > neotiv tests and the neotiv digital platform address key challenges of drug trials and diagnostic assessment in healthcare



Berron D, Cardenas-Blanco A, Bittner D, Metzger CD, Spottke A, Heneka MT, Fließbach K, Schneider A, Teipel SJ, Wagner M, Speck O, Jessen F, Düzel E, and the DELCODE study group. 2019. **Higher CSF tau levels are related to hippocampal hyperactivity and object mnemonic discrimination in older adults.** The Journal of Neuroscience.

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Let's talk about an individual solution for you

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