Mapping cognition along the continuum of Alzheimer's Disease:
Towards novel assessments, affordable biomarkers, and technology-driven interventions

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Workshop Outline

1. **Novel cognitive assessments for Alzheimer's disease: do we need a paradigm shift?**
2. **From cognitive markers to affordable biomarkers**
3. **Technology-driven and person-centred interventions**

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Workshop Activities

Introductory Lecture (30 min per topic)

We will start with a theoretical introduction to each topic of the workshop. These will focus on the status quo and recent research findings either challenging it or supporting it.

Group Discussions

Problem based (10 min per topic)

Each theoretical section will be followed by the discussion of a problem that has been acknowledged as a contemporary challenge. Groups will discuss these problems for about 10 min. You are expected to critically appraise the knowledge addressed throughout the theoretical discussion.

Project Ideas: overcoming barriers (10 min per topic)

Each topic will include the discussion of potential strategies that can help address an outstanding issues in the relevant area (i.e., the problem). Groups will be encouraged to engage in 10 min discussions aimed at generating ideas that could lead to feasible research projects.

Feedback Section
There will be 10 minutes for the groups to feed back to the class.

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Topic 1: Content

Novel cognitive assessments for Alzheimer's disease (AD): do we need a paradigm shift?

1. Cognition in AD
2. A good cognitive marker for AD
3. Novel cognitive assessments
4. The neuroanatomical evidence
5. Global challenges: e.g., hominization

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Novel cognitive assessments for Alzheimer's disease (AD)

1. Cognition in AD

Alzheimer's disease is a common neurodegenerative disorder responsible for progressive neuronal death which gradually impairs cognitive functions to the extent that precludes the ability to perform daily living functions and eventually the capacity to live independently.

1. **Late Onset Sporadic AD**
2. **Early Onset AD: Sporadic or Familial (PSEN 1 and 2, APP, and other gene mutations)**

In the last decade, a new disease model has been proposed (**Duboi et al., 2016**):

- ⓿ **Risk factor assessment (primary prevention)**
  - ❶ **Screening (early detection and early intervention: secondary prevention)**
    - ❷ **Diagnosis and staging**
      - ❸ **Treatments and monitoring of treatment effects**

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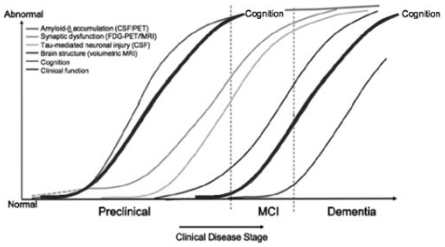
Novel cognitive assessments for Alzheimer's disease (AD)

1. Cognition in AD

The new model includes screening tests with high sensitivity, lower specificity, and low cost, to those with higher specificity and potential for longitudinal assessment (**Duboi et al., 2016**).

Available cognitive tests reliably detect changes only when clinical symptoms start.



(**Sperling et al., 2011**)

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Novel cognitive assessments for Alzheimer's disease (AD)

2. A good cognitive marker for AD (Logie et al., 2015)

- Not show effects of healthy aging
- Be sensitive and specific to the very early stages of AD
- Not show improvement solely as a result of repeated testing
- Be useable in primary care and in intervention trials with minimal training
- Avoid very low performance levels when the symptoms become severe
- Be targeted at cognitive impairments shown in AD but not in other disorders
- Be non-invasive with minimal discomfort to the patient
- Be quick to administer and inexpensive
- Be insensitive to the cultural background and literacy levels of those assessed

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Novel cognitive assessments for Alzheimer's disease (AD)

3. Novel cognitive assessments

"This review is a selective summary of several novel, potentially promising, approaches that are being explored for detecting early cognitive evidence of preclinical Alzheimer's disease in pre-symptomatic individuals".

… "Among the most interesting candidates for high specificity in the very early stages of disease are the Free and Cued Selective Reminding Test and the Visual Short-Term Memory Binding Test".

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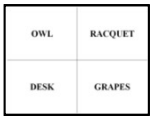
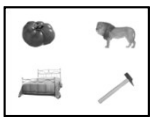
Novel cognitive assessments for Alzheimer's disease (AD)

3. Novel cognitive assessments

Fruit?
Sports Equipment?
Bird?
Furniture?





(e.g., Frasson et al., 2011)

The **Free and Cued Selective Reminding Tests (e.g., FCSRT and MCT or MBT)** begin with a study phase in which items (grapes) are identified in response to semantic cues (fruit) that are used in the test phase to prompt recall of items not retrieved by free recall.

These procedures ensure attention and appropriate semantic processing and maximize recall because the same cues are used in the study and test phases to provide encoding specificity.

(Buschke et al., 2017; Grober et al., 1988)

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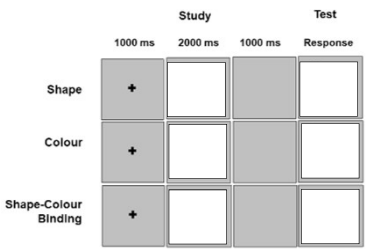
Novel cognitive assessments for Alzheimer's disease (AD)

3. Novel cognitive assessments



The **Short-Term Memory (STM) Binding Test** contrasts the ability to temporarily retain shape-colour combinations with the ability to retain just shapes or colours. The ability is assessed by detecting changes between an initial study display and a test display shown one second after.

This low-level visual integration function supports the conjunction of features into unified representations and recognition of objects' identity.

(**Parra et al., 2010**)

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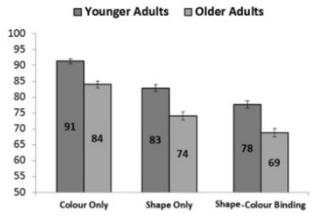
Novel cognitive assessments for Alzheimer's disease (AD)

3. Novel cognitive assessments



Evidence has now accrued supporting the notion that STM Binding is a function which does not show effects of healthy ageing.

This is true whether feature conjunction leads to the formation of meaningless or meaningful item representations in STM.

[Group x Condition: *F* = 0.34 , *p* = ns]

(**Brockmole et al., 2008; Parra et al., 2009; Van Geldorp et al., 2014**)

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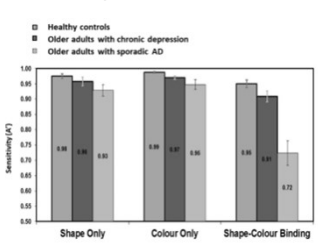
Novel cognitive assessments for Alzheimer's disease (AD)

3. Novel cognitive assessments



STM Binding is a function sensitive and specific to the very early stages of late-onset sporadic AD.

It unveils a cognitive impairment cause AD but not by other age-related disorders such as chronic depression.

The specificity of STM binding holds when assessing other forms of dementia such as FTD, VasD, PD, LBD.

[Group x Condition: *F* = 12.2, *p*<0.001]

(**Cecchini et al., 2017; Della Sala et al., 2012; 2016; Parra et al., 2010**)

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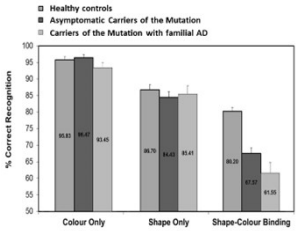
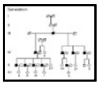
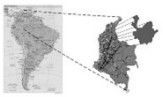
Novel cognitive assessments for Alzheimer's disease (AD)

3. Novel cognitive assessments



[Group x Condition: $F = 14.9$, $p<0.001$]





STM Binding is also sensitive to early-onset familial AD caused by the mutation E2980A-PSEN1.

Impaired binding abilities are observed in mild stages of dementia and in otherwise asymptomatic carriers.

Such binding impairments contrast with a completely normal neuropsychological background, including hippocampal-related memory functions (i.e., PAL).

(**Parra et al., 2010; 2011**)

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Novel cognitive assessments for Alzheimer's disease (AD)

3. Novel cognitive assessments

Unpublished evidence drawn from a larger sample of pre-symptomatic carriers (E280A-PSEN1) reveals:

1. No evidence of impairment using free and cued selective reminding procedures contrasting with STM binding deficits.
2. STM binding deficits appeared earlier than reported by Parra et al. (2010).
3. The STM task assessed reconstruction of feature conjunctions rather than change detection (see Jonin et al., 2018).

	Controls (n = 155)	E280A Carriers (n = 98)	t-Test *p-value*
Age	30.6 (9.8)	32.9 (8.5)	0.055
Education (years)	8.6 (4.3)	9.7 (4.4)	0.066
MMSE	29.3 (1.1)	29.4 (1.2)	0.466
STM Binding	64.6 (18.6)	58.5 (20.9)	**0.025**
MIS - Free Recall	6.9 (1.5)	6.9 (1.9)	0.910
MIS - Cued Recall	0.9 (0.6)	1.0 (0.9)	0.661
MIS - (A+B)	7.2 (1.2)	7.2 (1.4)	0.922
MCT - Cued Recall (List 1)	14.9 (1.4)	14.8 (2.0)	0.480
MCT - Cued Recall (List 2)	12.9 (2.7)	12.7 (3.4)	0.495
MCT - Cued Recall 2 (List 1)	14.2 (1.9)	13.9 (2.5)	0.373
MCT - Cued Recall 2 (List 2)	13.2 (2.7)	12.8 (3.1)	0.274
MCT - Cued Recall 2 (Lists 1 + 2)	27.3 (4.0)	26.7 (5.2)	0.269

MIS = Memory Impairment Screening; MCT = Memory Capacity Test

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Novel cognitive assessments for Alzheimer's disease (AD)

3. Novel cognitive assessments

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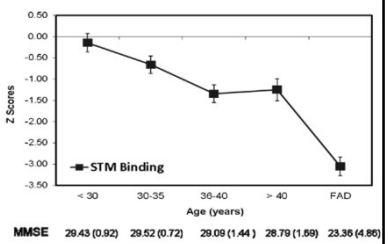

MMSE	29.43 (0.92)	29.52 (0.72)	29.09 (1.44)	28.79 (1.69)	23.36 (4.86)

Moreno et al. (2011). *Alzheimer's & Dementia*, 7(4), Supplement , Page S257

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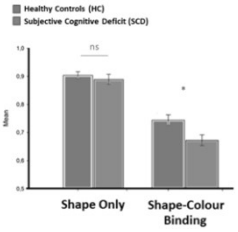
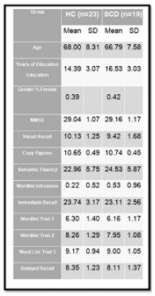
Novel cognitive assessments for Alzheimer's disease (AD)

3. Novel cognitive assessments



STM binding deficits are observed in older adults with Subjective Cognitive Decline (SCD) who still present with an intact neuropsychological profile and in patients with Mild Cognitive Impairment (MCI) to a greater extent.

SCD is associated to a high risk of developing MCI and amnestic MCI is linked to an even higher risk of developing AD dementia.



Group	HC (n=23)		SCD (n=19)	
	Mean	SD	Mean	SD
Age	68.00	8.31	66.79	7.58
Years of Education	14.39	3.07	16.53	3.03
Gender % Female	0.39		0.42	
MMSE	29.04	1.07	29.16	1.17
Visual Recall	10.13	1.25	9.42	1.68
Copy Figures	10.65	0.49	10.74	0.45
Semantic Fluency	22.96	5.75	24.53	5.87
Wordlist Intrusions	0.22	0.52	0.53	0.96
Immediate Recall	23.74	3.17	23.11	2.56
Wordlist Trial 1	6.30	1.40	6.16	1.17
Wordlist Trial 2	8.26	1.29	7.95	1.08
Word List Trial 3	9.17	0.94	9.00	1.05
Delayed Recall	8.35	1.23	8.11	1.37

(**Koppara et al., 2015**)

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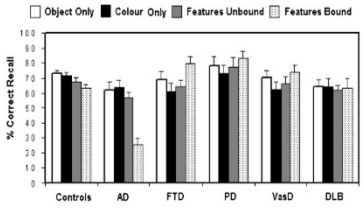
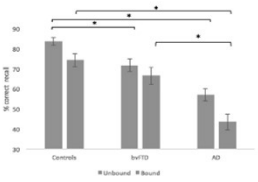
Novel cognitive assessments for Alzheimer's disease (AD)

3. Novel cognitive assessments

- STM binding impairments are found in AD but not in other dementias.



(**Della Sala et al., 2012**)



(**Cecchini et al., 2017**)

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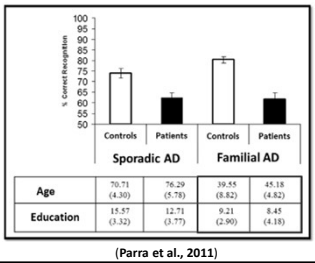
Novel cognitive assessments for Alzheimer's disease (AD)

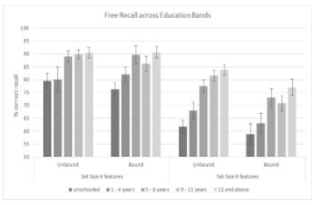
3. Novel cognitive assessments

- STM binding is insensitive to the cultural background and literacy levels of those assessed.



Age	70.71 (4.30)	76.29 (5.78)	39.55 (8.82)	45.18 (4.82)
Education	15.57 (3.32)	12.71 (3.77)	9.21 (2.90)	8.45 (4.18)

(**Parra et al., 2011**)



(**Yassuda et al., *submitted***)

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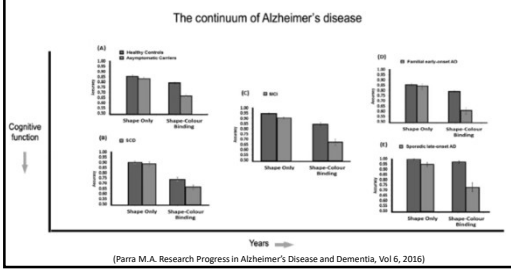
Novel cognitive assessments for Alzheimer's disease (AD)

3. Novel cognitive assessments



(Parra M.A. Research Progress in Alzheimer's Disease and Dementia, Vol 6, 2016)

STM binding deficits have now been observed along the continuum of AD.

It has been recently noted that when they appear in patients thought to be in the prodromal stages of AD (MCI), they are more likely to progress to the dementia stages.

(**Parra et al., 2018**)

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Novel cognitive assessments for Alzheimer's disease (AD)

3. Novel cognitive assessments

What properties of the STM binding test may grant such a reliability?

1. The memoranda is only held temporarily, needing little or no support from long-term memory.
2. Instead of associative memory, the STM binding test assesses low level visual integration (i.e., feature conjunctions).
3. Such low level visual functions have little reliance on literacy or education.
4. The test relies on a simple set of instructions, thereby limiting any challenge for people with little formal education.
5. It is not affected by prior knowledge, experience, or practice effects.
6. It seems to tap into the function of a brain network that remains functional (i.e., reorganises) across the lifespan but is affected by AD from its very early stages.

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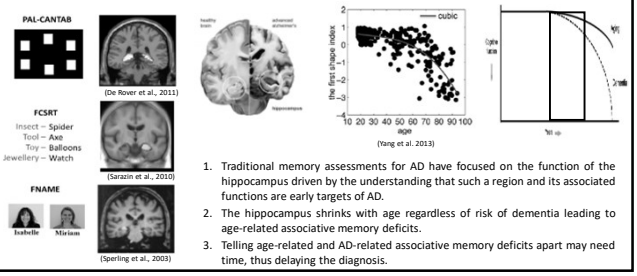
Novel cognitive assessments for Alzheimer's disease (AD)

4. The neuroanatomical evidence



1. Traditional memory assessments for AD have focused on the function of the hippocampus driven by the understanding that such a region and its associated functions are early targets of AD.
2. The hippocampus shrinks with age regardless of risk of dementia leading to age-related associative memory deficits.
3. Telling age-related and AD-related associative memory deficits apart may need time, thus delaying the diagnosis.

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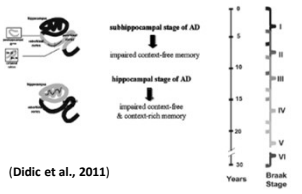
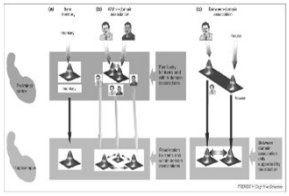
Novel cognitive assessments for Alzheimer's disease (AD)

4. The neuroanatomical evidence



(**Didic et al., 2011**)



Mayes, Montaldi & Migo, 2007

AD undergoes two stages, a sub-hippocampal and a hippocampal stage. The former is characterised by subtle memory changes, affecting context-free functions (e.g., item recognition, familiarity). The latter, is identified by the presence of context-rich memory impairments (episodic) which are more notorious and troublesome.

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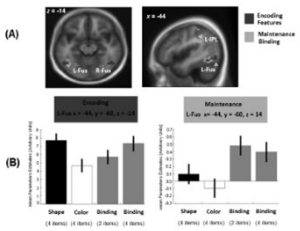
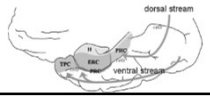
Novel cognitive assessments for Alzheimer's disease (AD)

4. The neuroanatomical evidence



(**Parra et al., 2014**)

- Healthy young adults performed the STM binding test during a fMRI session. Parietal-occipital-temporal regions were found active while they held feature bindings in STM.
- No hippocampal activity was found to be linked to task performance.
- Such binding-specific regions are part of the visual ventral stream known to support object recognition and which feeds into the medial temporal lobe via extrahippocampal regions affected in the sub-hippocampal stages of AD.



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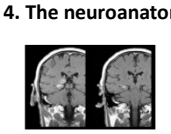
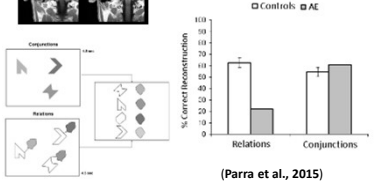
Novel cognitive assessments for Alzheimer's disease (AD)

4. The neuroanatomical evidence



<u>Case EA</u>: A 72 years-old patient who had a stroke that affected the right hippocampus and presented with amnesia.



(**Parra et al., 2015**)

Evidence from Single Case Studies has shed further light.

EA was asked to hold feature conjunctions or feature relations in STM and then reconstruct studied conjunctions or relations from two sets presenting the constituent features.

EA was able to reconstruct feature conjunctions. However, significant deficits were observed when the studied items were feature relations.

This was also true when conjunctions and relations had to be recalled.

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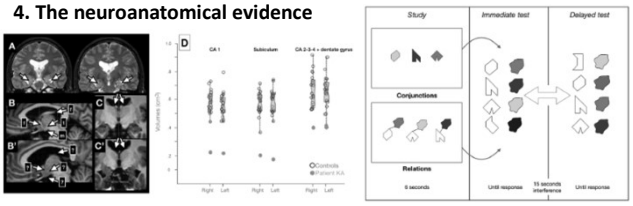
Novel cognitive assessments for Alzheimer's disease (AD)

4. The neuroanatomical evidence



KA is a 36 years-old man who suffered form neonatal hypoxia which severely damaged his bilateral hippocampal formation, causing severe atrophy of the fornix, bilateral anterior thalamic nuclei, mammillary bodies as well as the mammillo-thalamic tract. KA suffers from severe amnesia.

(**Jonin et al., 2018**)

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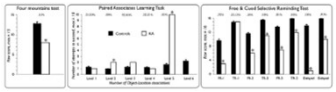
Novel cognitive assessments for Alzheimer's disease (AD)

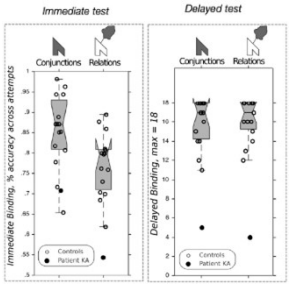
4. The neuroanatomical evidence



KA showed significant impairments in all the tasks currently suggested as markers for AD which assess associative LTM.

However, on repetitive testing, KA showed completely normal performance on the STM task that assesses feature conjunctions. His performance on the version of the STM task assessing feature relations was significantly impaired.

When KA was asked to hold conjunctions or relations in LTM, he showed significant impairments, in line with his amnesia.



(**Jonin et al., 2018**)

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Novel cognitive assessments for Alzheimer's disease (AD)

5. Global challenges (hominization and cross-cultural validation)

The need for harmonisation and innovation of neuropsychological assessment in neurodegenerative dementias in Europe: consensus document of the Joint Program for Neurodegenerative Diseases Working Group

… "Among the most interesting candidates for high specificity in the very early stages of disease are the FCSRT and the Visual Short-Term Memory Binding Test".

Neurology

Dementia in Latin America

Assessing the present and envisioning the future

… "We have identified regional gaps and strategies … … lack of culturally valid assessment procedures and reliable diagnostic markers which enable comparison of dementia figures among LAC and internationally".

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Final Comments - Topic 1

1. There is a need of a paradigm shift in understanding the assessment of cognitive functions to aid the early detection of AD.
2. Novel assessments should prioritise cognitive functions that are sensitive and specific to AD from the very early stages of its continuum.
3. Such impairments should not be accounted for by age or the level of education of the affected person.

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Problem-Based Activity

In the light of the evidence presented in the theoretical session, discuss the criteria of a good maker for AD. Are they attainable? Think of strategies that can be followed to develop assessment tools that would potentially meet such criteria?

Project Ideas: Overcoming Barriers

What strategies can be pursued to provide cognitive assessments that meet global needs? Could cognitive markers for AD which hold global validity be developed? How?

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Topic 2: Content

From cognitive markers to affordable biomarkers

1. The A-T-N framework
2. Where are we standing from a cognitive viewpoint?
3. New cognitive biomarkers
4. EEG Studies:
   - Lab based
   - Potable assessment
   - In-home assessment
5. Eye-tracking and cognition in AD
6. Peripheral Biomarkers for AD: New Biomarker Programs

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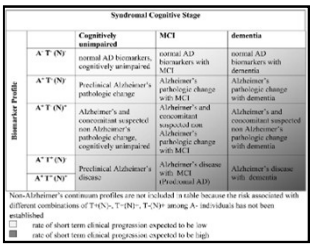
From cognitive markers to affordable biomarkers

1. The A-T-N framework



Biomarker Profile	Syndromal Cognitive Stage: Cognitively unimpaired	MCI	dementia
A⁻T⁻(N⁻)	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
A⁺T⁻(N⁻)	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
A⁻T⁺(N⁺) A⁺T⁺(N⁻) A⁺T⁺(N⁺)	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
A⁺T⁻(N⁺) A⁺T⁻(N⁻)	Preclinical Alzheimer's disease	Alzheimer's disease with MCI (Prodromal AD)	Alzheimer's disease with dementia

Non-Alzheimer's continuum profiles are not included in table because the risk associated with different combinations of T⁺(N⁺), T⁻(N⁺), T⁻(N)⁻ among A- individuals has not been established
□ rate of short term clinical progression expected to be low
■ rate of short term clinical progression expected to be high

… "Thus, non–biomarker studies can establish robust and valid associations between risk factors and **Alzheimer's clinical syndrome**, but the biologically based studies are needed to determine if these associations are with AD".

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From cognitive markers to affordable biomarkers

1. The A-T-N framework: challenges for LMIC

- Biomarker data (PET and CSF) can be difficult to acquire in some types of studies and in some geographic locations.
- Biomarker data mainly from selected participants recruited through tertiary care dementia centres.

Whether such recommendations can be harmonized across the developed and developing world is unclear at present.

- Cost-benefit: necessary access to equipment currently unavailable in most LAC.
- Limited budget available for research.
- Trade-off: quality of measurement and other desirable features of research such as geographic, socioeconomic, and racial diversity of sample participation as well as sample size, and response rates.

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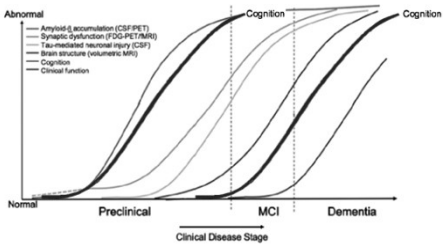
From cognitive markers to affordable biomarkers

2. Where are we standing from a cognitive viewpoint?

A-T-N Framework:

- Confirming the presence of cognitive impairment is essential to ascertain who is on the AD continuum.
- Such a confirmation is currently possible in patients with Mild Cognitive Impairment (i.e., Stage 3 of the novel Numeric Clinical Staging).

Are there subtle cognitive impairments which can be associated with early AD pathology?



(**Sperling et al., 2011**)

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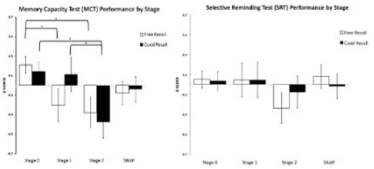
From cognitive markers to affordable biomarkers

3. New cognitive biomarkers

Stage 0: Aβ-/ND-
Stage 1: Aβ+/ND-
Stage 2: Aβ+/ND+
SNAP: (Suspected Non-Alzheimer's disease Pathology): Aβ-/ND+

1. **Selective Reminding Test (SRT)**
2. **Memory Capacity Test (MCT)**



(**Papp et al., 2015**)

Stage 1: reduction in MCT, free recall only.

Stage 2: more reliably detectable and more advanced memory decrements (a decline in both free and cued recall).

SNAP: trend towards lower free recall but not linked to cued memory decrements.

Diagnostic specificity of impaired <u>cued recall</u> to underlying AD pathology.

"… There are subtle, yet measurable memory decrements in normal older adults with biomarker evidence of preclinical Alzheimer's disease (AD)."

Cognitive Biomarkers

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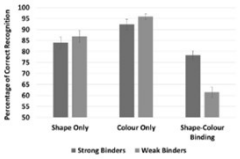
From cognitive markers to affordable biomarkers

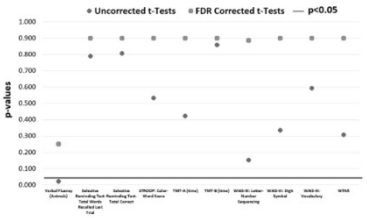
3. New cognitive biomarkers

A group of 40 healthy older adults [Age: 65.38 (3.06); Education in years: 16 (2.01); Gender M/F: 23/17] were recruited into the study.



Group x Condition [$F(2,74) = 23.49$; $p < 0.001$; $\eta^2 = 0.39$; $\beta = 1.0$]

(**Parra, Gazes & Stern, 2017**)



A cut-off score for the Cost of Binding (20%) (Koppara et al., 2015; Brockmole, et al., 2008) classified participants as Strong and Weak Binders. They did not differ on any other neuropsychological tests.

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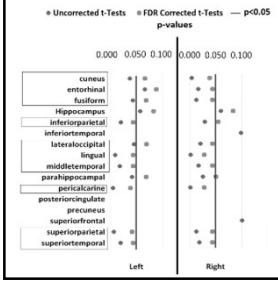
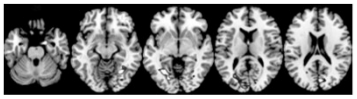
From cognitive markers to affordable biomarkers

3. New cognitive biomarkers





- Relative to Strong Binders, Weak Binders showed significantly larger deposits of Aβ along parietal-occipital-temporal regions.
- Volumetric and Cortical Thickness analysis did not yield significant between-group differences.
- STM Binding deficits in asymptomatic older adults were linked to increased amyloid deposits but not to atrophy or impairment on other neuropsychological functions.
- STM binding deficits are subtle, yet measurable memory decrements in normal older adults with biomarker evidence of preclinical Alzheimer's disease.

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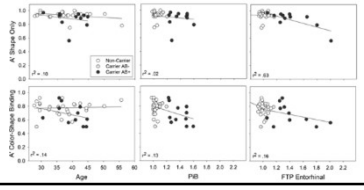
From cognitive markers to affordable biomarkers

3. New cognitive biomarkers

A group of 40 participants from the largest known kindred of individuals with high prevalence of the PSEN-1 E280A mutation.

16 carriers of the mutation: 12 were preclinical and 4 were early MCI
24 non-carriers healthy controls



- VSTM performance correlated strongly with tau in entorhinal cortex and inferior temporal lobe.
- Such correlations were less apparent with amyloid (disease stage?).
- Similar pattern of association was found for the delayed recall test from the CERAD.
- The results confirm VSTM's status as an early marker of AD pathology.

(**Norton et al, *submitted***)

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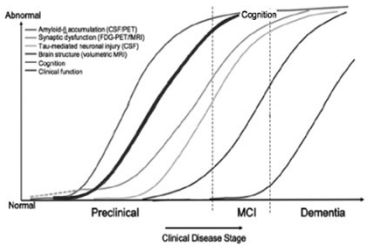
From cognitive markers to affordable biomarkers

3. New cognitive biomarkers

- Evidence in now accumulating indicating that there are cognitive functions which decline in the very early stages of AD.
- Such a decline is associated with the accumulation of abnormal proteins in the brain (i.e., amyloid & tau pathology) in still asymptomatic individuals.
- However, methods for tracing molecules are expensive, require highly specialised centres and staff, and are still widely unavailable.
- **Are there more affordable methods that could provide biological correlates of such cognitive impairments?**



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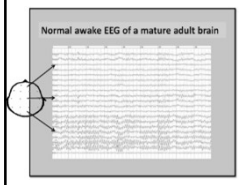
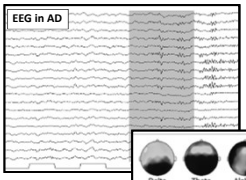
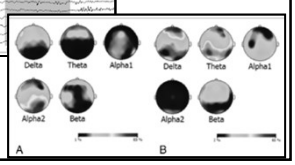
From cognitive markers to affordable biomarkers

4. EEG Studies: Lab based





AD progressive synaptopathology hampers the organization of the resting EEG whereby it becomes slow and undifferentiated from a frequency perspective.



When signals are analysed in the frequency domain, the EEG shows a reduction of activity in fast frequency bands with abundant activity in slow bands.

Such abnormalities are not specific to AD. Many neuropsychiatric disorders present with very similar EEG features.

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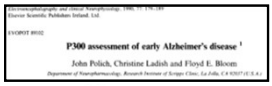
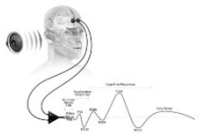
From cognitive markers to affordable biomarkers

4. EEG Studies: Lab based

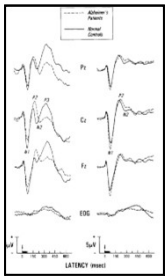

P300 assessment of early Alzheimer's disease [1]

John Polich, Christine Ladish and Floyd E. Bloom



Classical Odd-ball paradigm (auditory)

[SSSST. SSST, SST, ST, TTTTT, TTTT, TTT]



- One other EEG-based method is the extraction of Event Related Potentials (ERP), which are waveforms linked to specific sensory or cognitive functions.
- Such waveforms, known as ERP Components, are the electrophysiological correlates of cognitive functions sensitive to AD (i.e., attention, memory).
- However, cognitive functions which are specific to AD, remain a challenge.
- There is a need to identify cognitive functions sensitive and specific to AD whose EEG correlates could hold potential as disease biomarkers.

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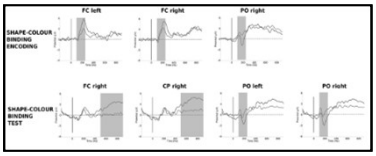
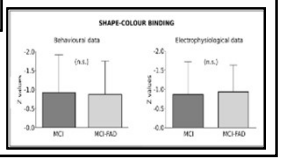
From cognitive markers to affordable biomarkers

4. EEG studies on STM binding: Lab based



A group of 13 sporadic MCI and 14 matched controls were contrasted with 10 familial MCI (E280A-PSEN1) and 10 matched controls.

Patients showed a very similar level of cognitive impairment which corresponded to multiple-domain amnesic MCI.



- The discrepancies (Z-values) during STM binding performance between sporadic MCI and their Controls and familial MCI and their Controls were undistinguishable from both a behavioural and an electrophysiological perspective.
- The latter suggests encoding dysfunctions elicited early over parietal-occipital and frontal regions.

(**Pietto et al, 2016**)

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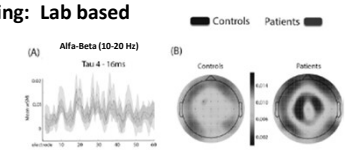
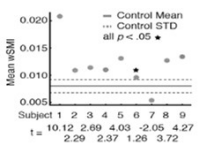
From cognitive markers to affordable biomarkers

4. EEG studies on STM binding: Lab based

The group of familial MCI (E280A-PSEN1) and matched controls were subjected to analysis of task-related brain connectivity.

As these patients have a less equivocal risk of dementia (100%), we investigated patterns of brain connectivity associated to STM binding performance.





- familial MCI patients showed increased connectivity during the encoding of feature bindings in STM.
- The increased connectivity seemingly reflects unsuccessful compensatory mechanisms triggered by the early stages of dementia.
- STM binding deficits in FAD seem to result from altered encoding mechanisms driven by dysfunction of a frontal-parietal-occipital network accompanied by aberrant compensatory mechanisms.

(**Parra et al, 2017**)

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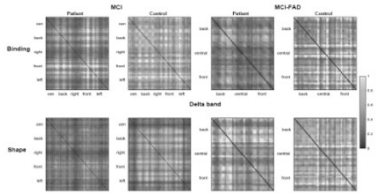
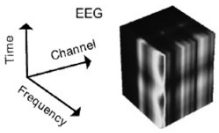
From cognitive markers to affordable biomarkers

4. EEG studies on STM binding: Lab based





A recent study applied complex tensor factorisation to decompose the EEG into scalp components described by the spatial, spectral, and complex trial profiles.

(**Spyrou et al, 2018**)

- The STM task yielded more distributed brain activation during the binding than the shape condition thus providing further evidence that binding entails connectivity between different brain areas which becomes weaker in prodromal AD.
- Lower power but higher synchronisation for sporadic than familial MCI: age-related compensatory changes leading to increased connectivity between brain areas as ageing progresses.

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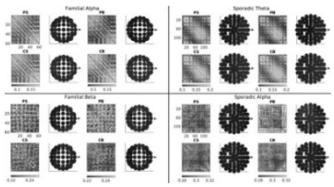
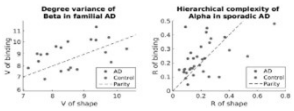
From cognitive markers to affordable biomarkers

4. EEG studies on STM binding: Lab based



How is hierarchical complexity of EEG activity affected in prodromal Alzheimer's Disease (AD)?



(**Smith et al, submitted**)

- Early and genetically driven AD pathology operating in younger brains alters the topology of a task-related network supporting VSTM binding by increasing its hierarchical spread (strength and recruitment) while in older brains experiencing MCI with unknown genetic factors, it hampers their hierarchical complexity. We can speculate that the latter indicates the additive effect of ageing on AD pathology.
- No age-related differences in connectivity measures other than activity in slower frequency bands in old age.

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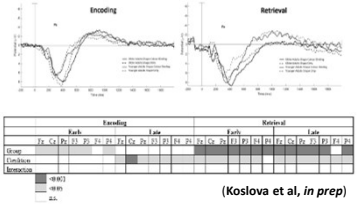
From cognitive markers to affordable biomarkers

4. EEG studies on STM binding: Potable assessment



(**Koslova et al, *in prep***)

We are interested in moving towards more portable EEG setups.

(**Cecchi et al., 2015**)

(1) Significant electrophysiological differences regardless of task condition: more recruitment in older adults.
(2) Effects more prominent during the retrieval phase of memory than during encoding (different from AD).
(3) Feature binding was found to be more resource demanding than single feature processing regardless of age.

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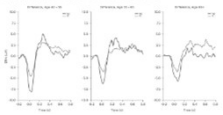
From cognitive markers to affordable biomarkers

4. EEG Studies: In-home assessment

BRAINWAVEBANK



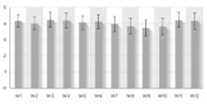


Figure 11. Bar chart illustrating adherence to trial protocol over 3 months of use. Mean number of sessions per week, error bars represent 95% CI.

Enabling daily, remote-monitoring of cognitive well-being has implications for large-scale screening at the earliest stages of neurodegeneration, and may allow for more proactive management.

To test the feasibility of gathering research-relevant EEG data using mobile dry-sensor technology in an unsupervised home environment.

Cloud-based analytics made individual predictions about age and cognitive performance.

Buick, McGuinness, Passmore, & Murphy. BrainWaveBank

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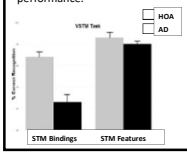
From cognitive markers to affordable biomarkers

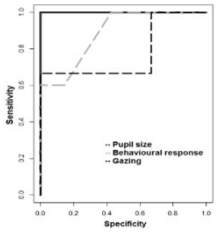
5. Eye-tracking and cognition in AD

Data were collected from 18 healthy older adults (HOA) and 18 age and education matched patients with AD. We used EyeLink 1000 eyetracker to collect oculomotor data during STM performance.

VIEWMIND



(**Fernández et al., 2018 a & b**)



- Oculomotor behaviours during the STM binding task reliably identified patients with AD.
- Pupil Size achieved better classification than both Behavioural and Gazing measures.
- Combining STMB performance and pupil behaviours offers biomarker evidence of AD pathology.

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From cognitive markers to affordable biomarkers

6. Peripheral Biomarkers for AD: future and opportunities

Alzheimer's Drug Discovery Foundation

DIAGNOSTICS ACCELERATOR: PERIPHERAL BIOMARKERS PROGRAM

Advancing Peripheral Biomarkers for Alzheimer's and Related Dementias

https://www.aldiscovery.org/research-and-grants/funding-opportunities/diagnostics-accelerator

Blood and other peripheral markers, including saliva, urine, and ocular biomarkers are encouraged.

- To support the development of affordable and accessible biomarkers for AD and related dementias.
- Aims to challenge the research community to develop novel biomarkers from peripheral modalities.
- Peripherally-sourced biomarkers will enable greater patient tolerability, integration with existing sample testing infrastructure, and the scalability and affordability necessary for population-level screening.
- They may, at a minimum, screen for the need to do more invasive CSF testing or expensive PET imaging.

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Final Comments - Topic 2

1. The discovery of cognitive functions which are sensitive and specific to AD from its preclinical stages opens new opportunities for screening.
2. As these subtle cognitive changes are associated with abnormal accumulation of brain proteins linked to AD, it is possible to consider tests assessing them, cognitive markers for AD.
3. Combined with affordable methodologies, such cognitive markers can provide biological evidence of AD pathology. These new developments will need further validation in larger trials.

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Problem-Based Activity

What limitations would such new technological developments face to be widely implemented (both in HIC and LMIC)?

Project Ideas: Overcoming Barriers

Based on the evidence discussed in the theoretical session (affordable biomarker solutions) how you envisage such new cost-effective technologies could be inserted in the health care pathway?

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Topic 3: Content

Technology-driven and person-centred interventions

1. Prothesis vs Enabler / Aiding vs Empowering
2. New technologies for dementia: recent evidence
3. Limitations and challenges
4. Experiences in the use of elements of Virtual Reality in the study of cognition in ageing:
   - Predictors of performance in real and virtual scenarios across age
   - Unveiling the cognitive underpinnings of instrumental activities of daily living in real and virtual environment across age
5. Global funds to support technological challenges

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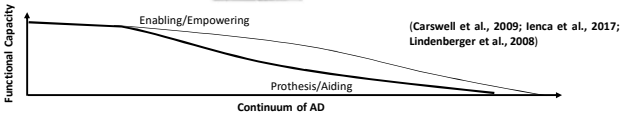
From cognitive markers to affordable biomarkers

1. Prothesis vs Enabler / Aiding vs Empowering

The Technology section of the Scotland's National Dementia Strategy 2017-2020 states that the Technology Charter will ensure that everyone with a diagnosis of dementia and those who care for them are aware of, and have access to, a range of proven technologies <u>to enable people living with dementia to live safely and independently</u>.



(**Carswell et al., 2009; Ienca et al., 2017; Lindenberger et al., 2008**)

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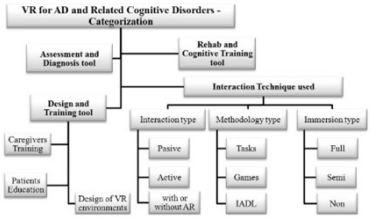
From cognitive markers to affordable biomarkers

2. New technologies for dementia: recent evidence



(**Garcia-Betances et al., 2015**)

- Technology-driven training can improve speed of processing in older adults and reduce dementia risk (Edwards et al., 2017).
- Daily living functions assessed in Virtual Environments correlate with outcomes from functional scales (Tarnanas et al., 2013).
- Technology-driven applications can be tailored for assessments and interventions of patients with dementia or at risk of dementia to meet their cognitive, physical, and emotional needs (Lenca et al., 2017).

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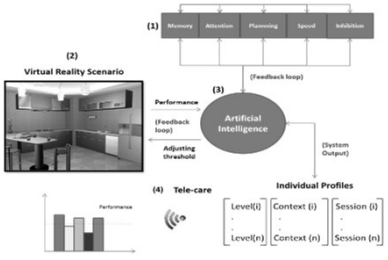
From cognitive markers to affordable biomarkers

2. New technologies for dementia: recent evidence

- Serious Games recreate a functional environment where patients can encounter difficulties similar to those found in real life.
- They are valid evaluation instruments for iADL and for cognitive screening.
- They record complete performance, are of easy administration, promote motivation, and are fun, thus leading to engagement and compliance.

However, VR still faces important limitations.

(**Vallejo et al., 2017**)



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From cognitive markers to affordable biomarkers

3. Limitations and challenges

1. Lack robust theories from cognition.
2. Lack meaningfulness and true ecological validity.
3. Fail to meet the changing needs of patients with neuroprogressive disorders.
4. Not always friendly, users need to comply rather than the other way round, thus preventing treatment adherence.
5. Still have important ethical and cultural limitations.

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From cognitive markers to affordable biomarkers

3. Experiences in the use of elements of Virtual Reality in the study of cognition in ageing: Predictors of performance in real and virtual scenarios across age

This study was aimed at investigating age-related changes in functional abilities and their associated cognitive underpinnings during task performance in virtual and real environments.

(**Parra & Kaplan, 2019**)

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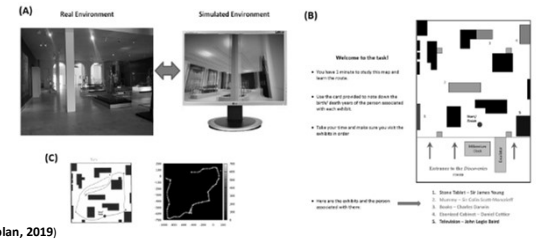
From cognitive markers to affordable biomarkers

3. Experiences in the use of elements of Virtual Reality in the study of cognition in ageing: Predictors of performance in real and virtual scenarios across age



(**Parra & Kaplan, 2019**)

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	Older group (n=21)			Younger group (n=22)		
	Range	M	SD	Range	M	SD
Overall IT usage						
Years***	0-52	**25.53**	13.90	0-25	**13.17**	8.30
Experience*	8-60	**32.10**	17.98	20-61	**42.55**	11.93
Ratio (experience/years)	0-8.4	**1.49**	1.69	0-78	**5.59**	16.22

Note: Student's t-test performed between older and younger adults; *p<0.05, **p<0.01, ***p<0.001

(**Parra & Kaplan, 2019**)

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3. Experiences in the use of elements of Virtual Reality in the study of cognition in ageing: Predictors of performance in real and virtual scenarios across age

Key findings:

1. Testing environment effected efficiency but not accuracy (longer distances in RE than in VE).
2. Task order effect (when RE first better performance than when VE first).
3. Older adults showed similar accuracy and efficiency to younger adults but needed more cognitive resources (visuospatial abilities).
4. Older adults' performance correlated with Activities of Daily Living.
5. Knowledge transfer between RE and VE in younger but not in older adults.

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From cognitive markers to affordable biomarkers

3. Experiences in the use of elements of Virtual Reality in the study of cognition in ageing: Unveiling the cognitive underpinnings of instrumental activities of daily living in real and virtual environment across age

VRAIS – Virtual Reality Assessment and Intervention System

This project investigated the cognitive profiles that characterise the normal age-related decline of IADL. We aimed to gather evidence of the cognitive functions that account for successes and failures during IADL performance across age.

(**Parra et al., *in prep***)

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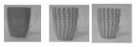
Subtask 1: Prepare a cup of tea	Item
1. Take the kettle	
2. Turn on the water tap	
3. Fill the kettle	
4. Turn on the kettle to boil water	
5. Take a tea cup - black with white circles	
6. Put a tea cup on the counter top	
7. Pick up a Yorkshire tea bag	
8. Put a tea bag into the teacup	
9. Take the kettle	
10. Put boiling water into the cup	



Perceptual/Episodic

Conceptual/Semantic

Unexpected interferences

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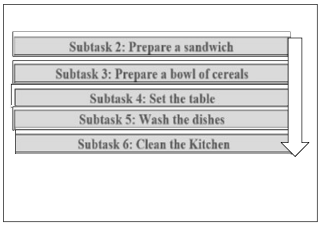

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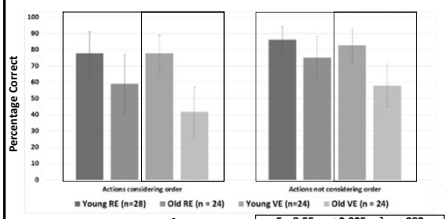
From cognitive markers to affordable biomarkers

3. Unveiling the cognitive underpinnings of instrumental activities of daily living in real and virtual environment across age



$F = 9.18$, $p < 0.005$, $\eta^2_p = .087$

$F = 8.55$, $p < 0.005$, $\eta^2_p = .082$

$F = 1.755$, $p = 0.188$, $\eta^2_p = .018$

Older adults performed more poorly than younger adults.

The age-related decline was more pronounced when:

- Serial recall of actions was considered.
- The task was performed in the virtual environment.

These effects were independent.

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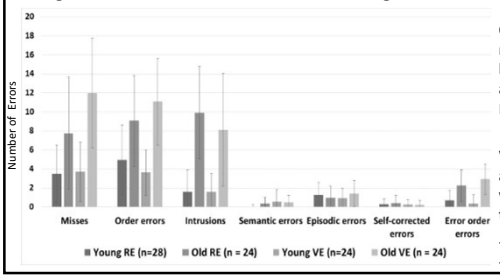
From cognitive markers to affordable biomarkers

3. Unveiling the cognitive underpinnings of instrumental activities of daily living in real and virtual environment across age



Older people missed more tasks. They also had more intrusions and order errors (VE > RE).

Was this because aspects of the task were unfamiliar to them?

- Unfamiliar sequence.
- Unfamiliar items.

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From cognitive markers to affordable biomarkers

3. Unveiling the cognitive underpinnings of instrumental activities of daily living in real and virtual environment across age

Table 5. *The number of misses, unrelated intrusions and related intrusions made by healthy younger and older adults on the everyday kitchen tasks in either the real environment or the virtual (VR) environment.*

	Real environment		VR environment		Main analysis			Post-hoc comparisons			
	Young (n=28) Mean (SD)	Old (n = 24) Mean (SD)	Young (n=24) Mean (SD)	Old (n = 24) Mean (SD)	Group	Environment	Interaction	$Y_{Real} - O_{Real}$	$Y_{VR} - O_{VR}$	$Y_{Real} - Y_{VR}$	$O_{Real} - O_{VR}$
					F, p, η^2_p	F, p, η^2_p	F, p, η^2_p	p, d	p, d	p, d	p, d
Misses	3.50 (3.06)	7.75 (5.89)	3.71 (3.13)	12.00 (5.77)	**F = 46.05, $p < .001$,** $\eta^2_p = .324$	**F = 5.819, $p < 0.05$,** $\eta^2_p = .057$	**F = 4.78, $p < 0.05$,** $\eta^2_p = .047$	**$p < .01$,** $d = 0.38$	**$p < .001$,** $d = 0.63$	$p = 1.00$, $d = 0.03$	$p < .05$, $d = 0.28$
Unrelated intrusions	0.39 (0.63)	2.04 (2.26)	1.13 (1.80)	1.92 (1.98)	F = 12.18, **$p = 0.001$,** $\eta^2_p = .113$	F = 0.754, $p = 0.387$, $\eta^2_p = .008$	F = 1.502, $p = 0.223$, $\eta^2_p = .015$	**$p < .005$,** $d = 0.96$	$p = .154$, $d = 0.35$		
Related intrusions	1.21 (1.85)	8.00 (4.78)	0.58 (1.18)	6.25 (5.43)	F = 69.65, **$p < 0.001$,** $\eta^2_p = .421$	F = 2.548, $p = 0.114$, $\eta^2_p = .026$	F = 0.563, $p = 0.455$, $\eta^2_p = .006$	**$p < .001$,** $d = 1.76$	**$p < .001$,** $d = 1.41$		

Note 1: Post-hoc Bonferroni correction for multiple comparisons leads only to a significant result if the p-value is below 0.0083 (0.05 / 6 comparisons).
Note 2: Significant findings are indicated in **bold.**

Older adults tended to replace unfamiliar tasks/items with tasks/items familiar to them.

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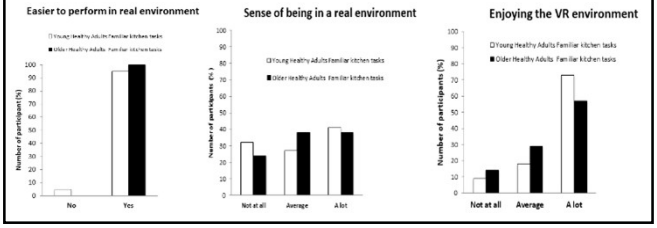
Subjective experiences



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Final Comments - Topic 3

1. VR applications offer reliable tools to assess functional abilities (IADL) in older people.
2. Older people's experiences, preferences, and cognitive abilities need to be considered and incorporated in such tools.
3. Meaningful VE can offer optimal scenarios to assess the cognitive underpinnings of functional decline in old age.
4. Future research should focus on how to enhance meaningfulness, personalization, and optimal interfaces for visualization and interaction.

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Problem-Based Activity

What advantages would an IT-based person-centred assessment and intervention program (e.g., Serious Games) have over traditional game-based training systems?

Project Ideas: Overcoming Barriers

What barriers could preclude the implementation of IT-based person-centred assessment and intervention programs and what strategies could help overcome them?

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Final Remarks

1. A paradigm shift in the development of cognitive tests for AD is currently needed. Novel tests should aim at subtle and domain-specific cognitive decline which although unnoticed by the effected individual, it results from underlying AD pathology (subclinical).
2. Novel affordable cognitive biomarkers can be developed by recording physiological activity linked to performance on the above mentioned tests.
3. Knowledge about the earliest cognitive impairments that lead to functional decline needs to be incorporated in technology-driven interventions to truly achieve a person-centred approach which can empower patients and enable them to function independently for longer.

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Thank you

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