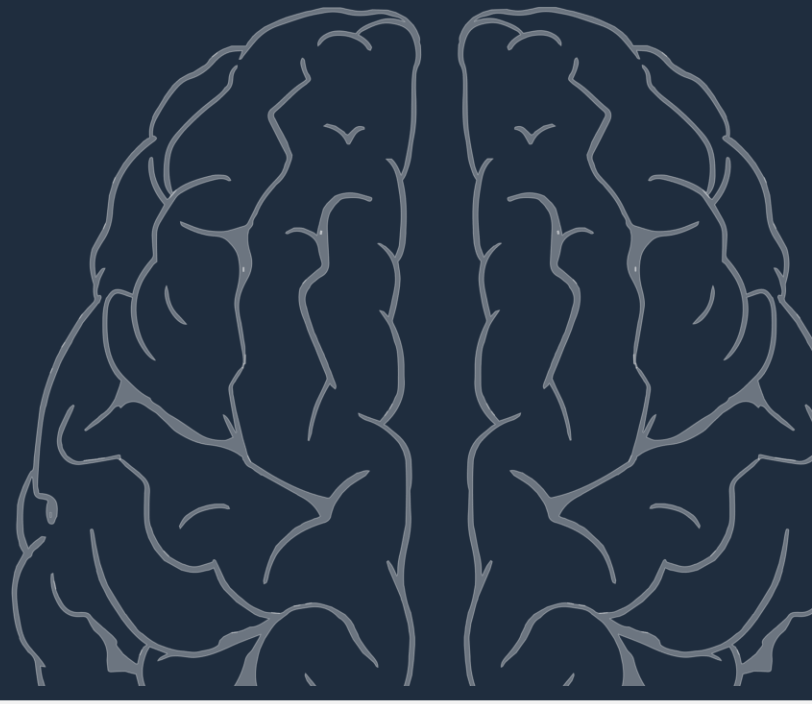
36th Annual meeting of the GRAL
Barlow Neurological Institute, January 28-31st 2025

Cognitive Intervention in Prodromal Alzheimer's Disease and At-Risk Older Adults: From Efficacy to Implementation



Sylvie Belleville PhD, MACSS FCAHS

FULL PROFESSOR, Département de Psychologie, Université de Montréal
CANADA RESEARCH CHAIR in Cognitive neuroscience of aging and brain plasticity
RESEARCHER, Centre de recherche de l'Institut universitaire de gériatrie de Montréal,
CIUSSS Centre-Sud-de-l'île-de-Montréal.
DIRECTOR Quebec Aging Network

Centre de recherche iugm Institut universitaire de gériatrie de Montréal

Labo Belleville Lab

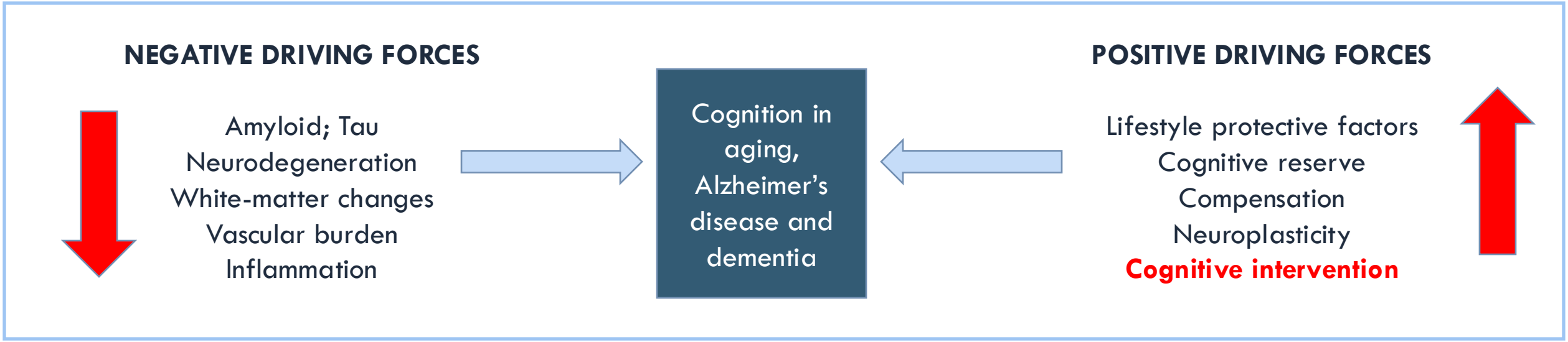
Université de Montréal

Centre intégré universitaire de santé et de services sociaux du Centre-Sud-de-l'île-de-Montréal
Québec

DISCLOSURES

- ✓Consultant for Lucilab and Innovatek International
- ✓Funding received from Mind Maze for SFL project
- ✓Creator of MEMO program, Atelier de Stimulation cognitive, Brain Health PRO and e-space

A balance between negative and positive drivers



NIH STAGE MODEL FOR BEHAVIORAL INTERVENTION DEVELOPMENT

COGNITIVE INTERVENTIONS

COGNITIVE TRAINING

- Behavioral approaches designed to improve or optimize cognition with practice and exercises.

TWO COGNITIVE TRAINING APPROACHES: DIFFERENT TRANSFER + MECHANISMS

Willis & Belleville, 2016

Strategy-oriented approach :

- Explicit learning of how and when to apply new or alternative methods for performing a particular task.
- Involves some form of metacognitive training.
- Aims to compensate for an impaired cognitive process by relying on intact ones.
- A positive effect expected for material amenable to the strategy.
- Context transfer: used in real life.

Process-based approach :

- Repeated or adaptive practice of computerized tasks to improve a core cognitive process.
- Restorative: improve an impaired cognitive process.
- Content transfer: transfer to tasks relying on the improved process

STRATEGY-ORIENTED APPROACHES	**TYPE OF EXERCISES**	**SAMPLE OF STUDIES**
Episodic memory	Imagery-based mnemonics, grouping, semantic elaboration, strategy adaptation	Yesavage, 1984; Stiggsdotter-Neely & Backman, 1995; Belleville et al, 2006; Hampstead, 2012; 2017; Botirolli et al, 2013; Bahar-Fuchs et al, 2013, 2019; Simon et al, 2020; Strickland-Hughes & West. 2022.
Reasoning	Regularity detection, reference training	Willis et al, 1981; Baltes et al, 1986; Willis et al, 2006
Prospective memory	Implementation-intention (verbalization of actions), planning aids (e.g. structuring of plans)	Chasteen et al, 2001; Kliegel et al, 2007; 2011; Zimmerman & Meyer, 2010; Herring et al, 2014
Multi-tasking	Task monitoring and flexibly change priority allocation in dual-task	Kramer et al, 1995; 2008; Bherer et al. 2005, 2006; Gagnon & Belleville, 2012; Bier et al, 2014; Simon et al, 2022,
PROCESS-BASED APPROACHES	**TYPE OF EXERCISES**	**SAMPLE OF STUDIES**
Working memory	Adaptive practice of different versions of updating tasks	Jaeggi et al, 2008; Buschkuehl et al., 2008; Buschkuehl et al., 2008; Dahling et al, 2008
Processing speed	Useful field of view, visual search, action videogames	Ball & Owsley, 1993; Ball et al, 2002; Bediou et al, 2018, Edward et al, 2018
Inhibition and shifting	Repeated practice	Karbach & Kray, Hartmann et al, 2016
Episodic memory	spaced learning and retrieval, increase memory load, repetition-lag	Logan & Balota, 2008; Jenning & Jacoby, 2003; Anderson et al, 2018; Boller et al, 2012

MEMO : A STRATEGY MEMORY TRAINING FOR OLDER ADULTS WITH MCI

(Gilbert, Fontaine & Belleville, 2007)

Focuses on **memory** : main complaint, main deficit.

Provides a **range** of **strategies** known to increase elaborate encoding + rely on preserved capacities (semantic, visual imagery). People with MCI can learn new strategies.

Relatively **short program** (six to eight 2-hour sessions with boosters).

Therapist-based small group (4-5 people) - allows individual guidance + social contact, healthy emulation.

Designed to promote **self-efficacy** (positive information on aging, modeling, gradual difficulty levels).

Instructions and exercises to help **use strategies in appropriate conditions in everyday life** and **to select and adapt strategies** (homework, real-life, instructions on when to use and not use the strategies).

THE MEMO+ STUDY

A three-arm 6-month single-blind randomized controlled trial in persons with MCI

1. COGNITIVE TRAINING-MEMO
2. PSYCHOSOCIAL INTERVENTION (Active control)
3. WAIT LIST

- 145 persons with mild cognitive impairment.
- 16 hours of training (8 weekly sessions) + booster.
- PRE; Post 3 months; Post 6 months.

MEMO+: Efficacy, Durability and Effect of Cognitive Training and Psychosocial Intervention in Individuals with Mild Cognitive Impairment

Sylvie Belleville, PhD, Carol Hudon, PhD,† Nathalie Bier, PhD,* Catherine Brodeur, MD,* Brigitte Gilbert, PhD,* Sébastien Grenier, PhD,* Marie-Christine Ouellet, PhD,‡ Chantal Viscogliosi, PhD,§ and Serge Gauthier, MD¶*

Programme d'intervention cognitive pour les aînés MEMO

PROTOCOL-ONLY PAPER

Measuring the impact of cognitive and psychosocial interventions in persons with mild cognitive impairment with a randomized single-blind controlled trial: rationale and design of the MEMO+ study

JAGS 66:655–663, 2018

Nathalie Bier,[1,2] Sébastien Grenier,[1,10] Catherine Brodeur,[3,4] Serge Gauthier,[4,5] Brigitte Gilbert,[1] Carol Hudon,[6,7] Émilie Lepage,[1] Marie-Christine Ouellet,[7,8] Chantal Viscogliosi[9] and Sylvie Belleville[1,10]

MEMO: A STRATEGY-BASED MEMORY TRAINING PROGRAM

GILBERT, FONTAINE & BELLEVILLE (2007)

Structured teaching and training on memory strategies

- Interactive imagery (1 session)
- Method of Loci (1 session)
- Face-name association (1 session)
- Text hierarchization (1 session)
- Semantic organization (1 session)

Pre-training

- Mental imagery and attention control (3 sessions)

Self-efficacy and transfer to real life

- Psycho-education
- Gradual increase of difficulty level
- Modeling and group exercises
- Homework + when to use vs not use the strategy

ACTIVE CONTROL: PSYCHOSOCIAL INTERVENTION

Ouellette, Grenier & Ducharme (2010)

Based on the cognitive-behavioural approach.

Designed to improve general well-being, prevent psychological distress and increase social networking.

- Psychoeducation
- Solution focused training
- Cognitive restructuring
- Diaphragmatic breathing
- Behavioral activation
- Anger management
- Problem-solving skill training

MEMO: A STRATEGY-BASED MEMORY TRAINING PROGRAM

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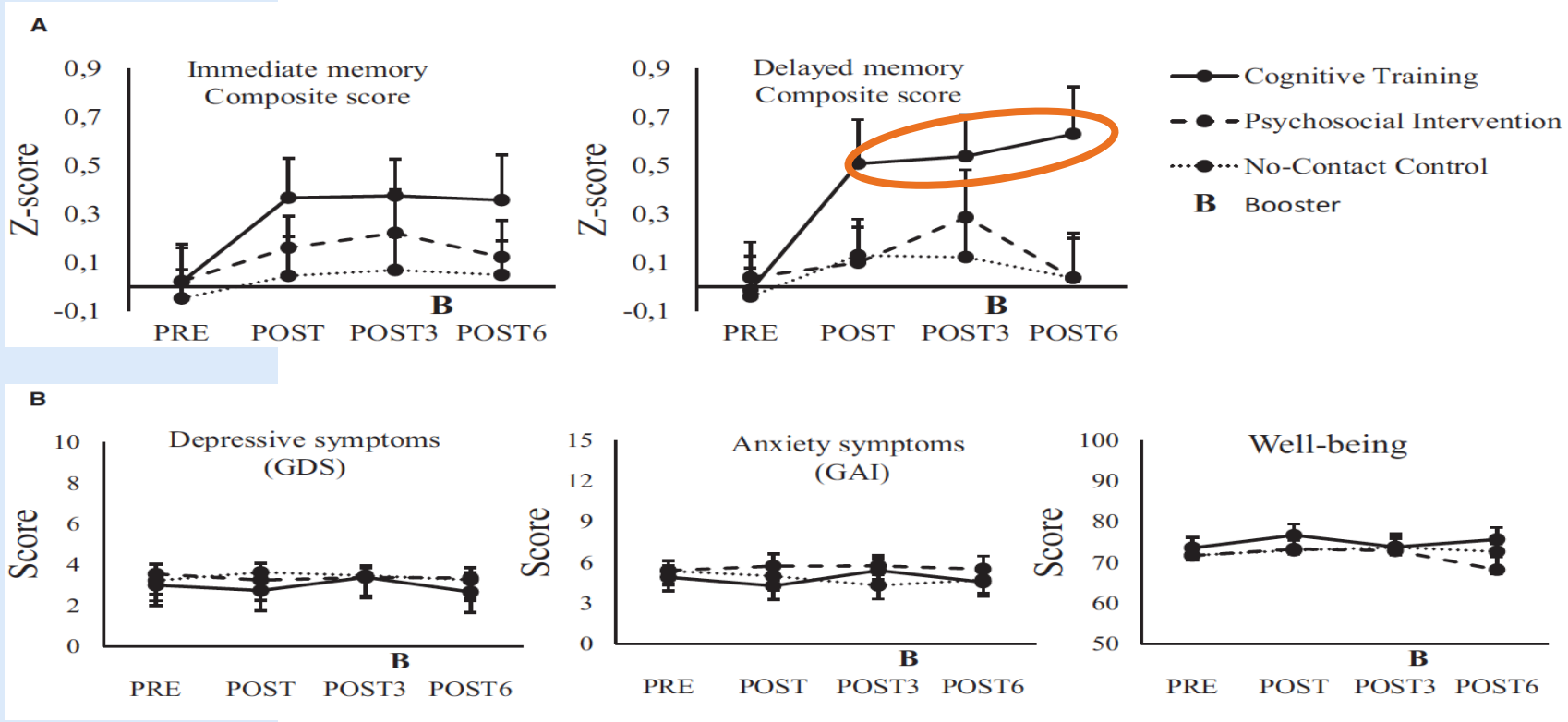
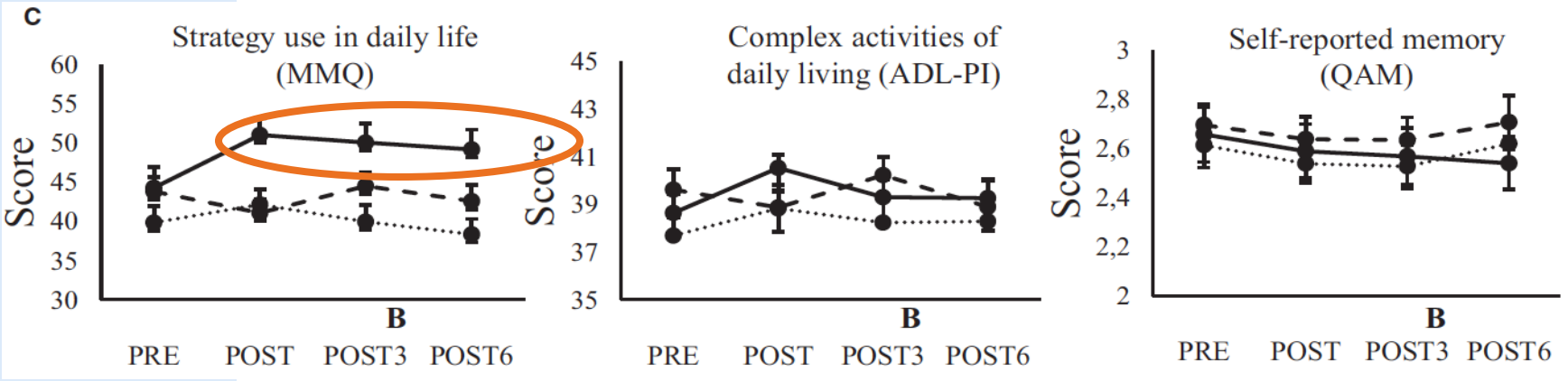
POSITIVE EFFECT ON DELAYED MEMORY AND CONTEXT TRANSFER



Modified ITT analyses; Mixed linear model adjusted for sex, educations and age;
Group x Time interaction; $P<0.01$, for delayed memory composite

Mean Age: 72.3; Mean Education: 14.6; 53.4% women

GENERALIZATION



Modified ITT analysis with mixed linear model adjusted for sex, age and education; Group x Time interaction; P<0.01 for strategy use (MMQ)

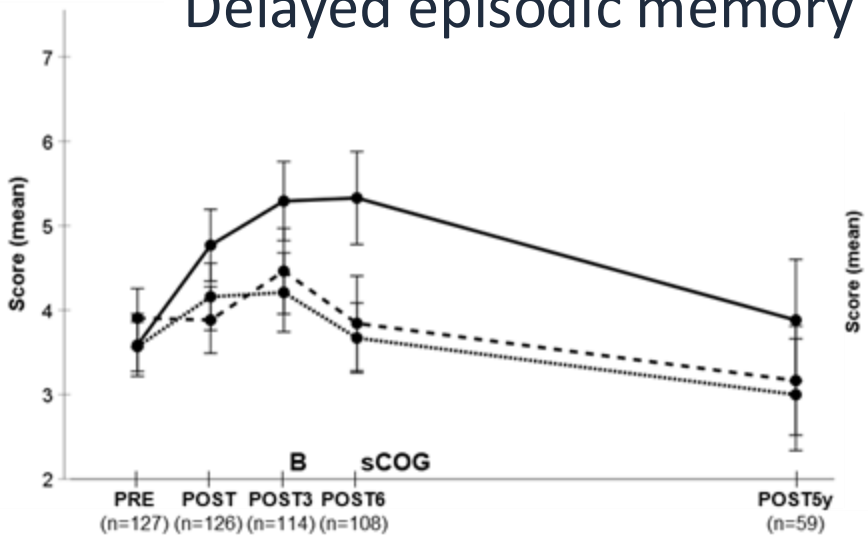
INDIVIDUAL VARIABLES: CHANGE SCORES ASSOCIATED WITH COGNITIVE STYLE AND SELF-EFFICACY

- **Larger routinization** → **predicts efficacy at post** (9% variance)
- **Greater self-efficacy, routinization and baseline memory** → **predicts 3-month durability** (32% variance)
- **Greater self-efficacy and routinization** → **predicts 6-month durability** (26% variance)

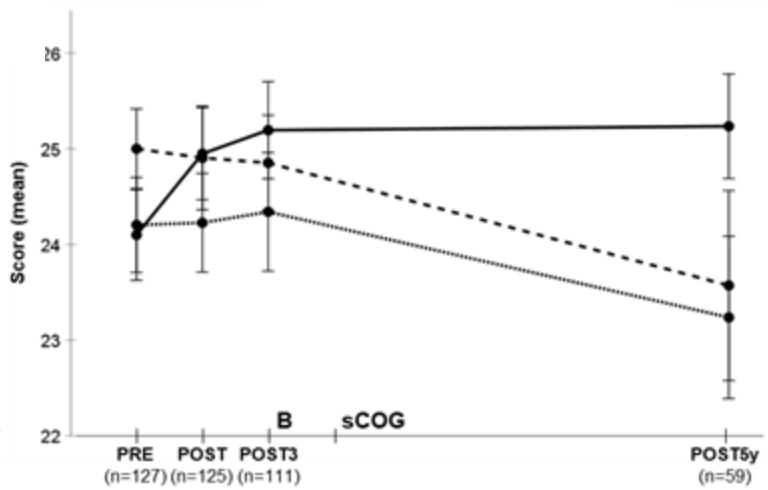
5-YEAR MAINTENANCE AND EFFECT ON MoCA

Cognitive Training
Psychosocial Intervention
No-Contact Control
B Booster
sCOG Optional Short Cognitive Training

Delayed episodic memory



MOCA



59 participants

Modified Intention to treat (ITT)
Mixed linear model Group x Time interaction for Delayed episodic memory and MoCA; p<0.001

No more group differences on **strategy use** due to decrease use in the cognitive training group and an increased use in controls

DOI: 10.1002/dad2.12626

RESEARCH ARTICLE

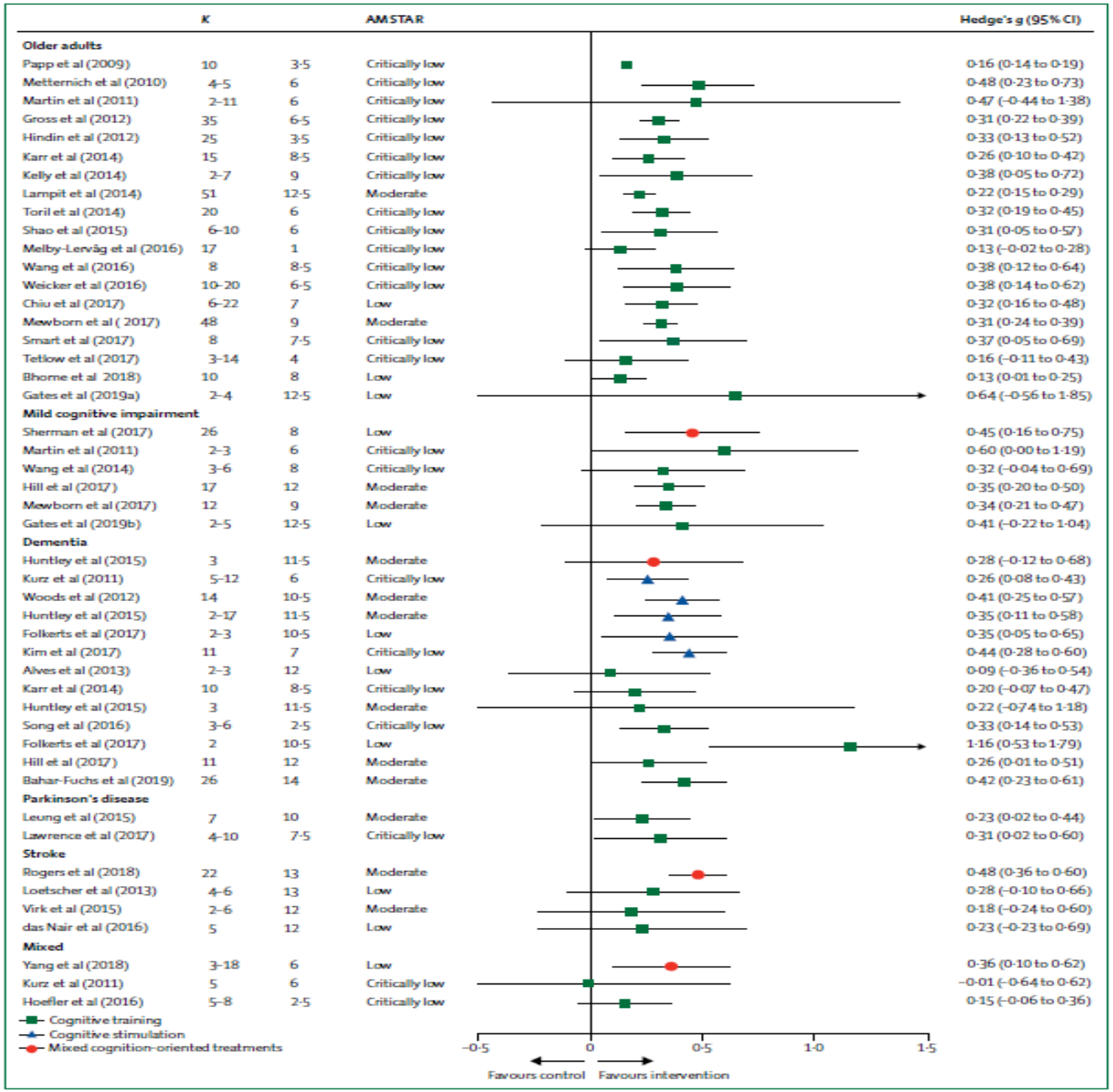
Diagnosis, Assessment & Disease Monitoring

Five-year effects of cognitive training in individuals with mild cognitive impairment

Sylvie Belleville[1,2] | Marc Cuesta[1] | Nathalie Bier[1,2] | Catherine Brodeur[1,2] | Serge Gauthier[3] | Brigitte Gilbert[1] | Sébastien Grenier[1,2] | Marie-Christine Ouellet[4] | Chantal Viscogliosi[5] | Carol Hudon[4,6]

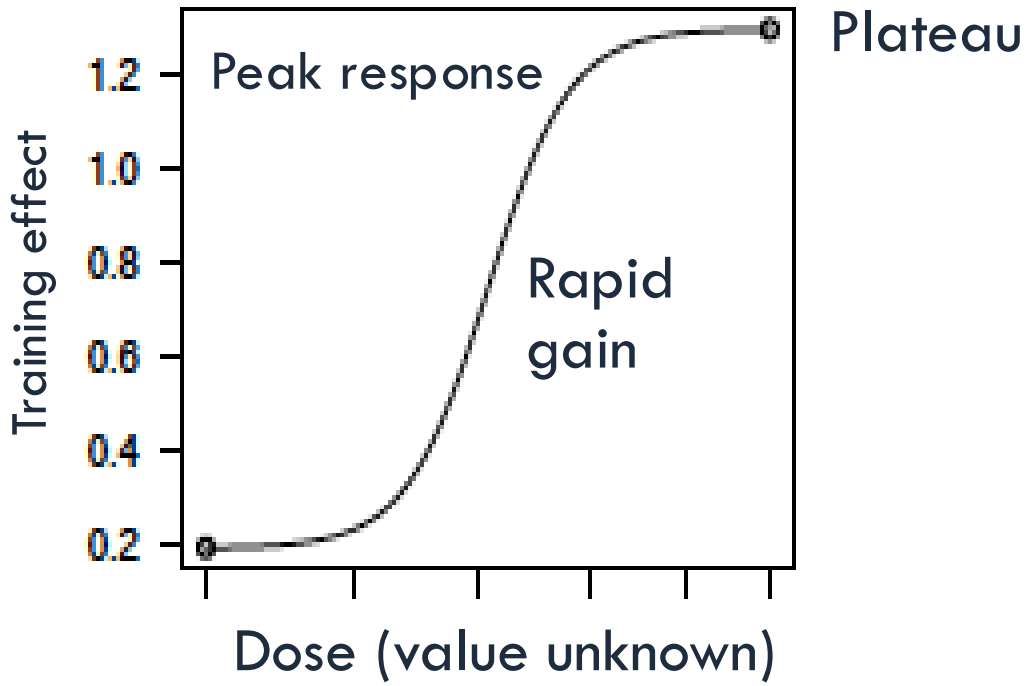
Alzheimer's Dement. 2024;16:e12626.
https://doi.org/10.1002/dad2.12626

Cochrane review on cognitive training in older adults



Bahar-Fuch, 2022

WHAT IS THE RIGHT DOSE?



When does the dose become therapeutic?

When does an additional dose no longer provide additional benefits?

Do different individuals require different dose?

DATA from MAPT Study

Is more always better? Dose effect in a multidomain intervention in older adults at risk of dementia

Sylvie Belleville[1,2] | Simon Cloutier[1,2] | Samira Mellah[1] | Sherry Willis[3] | Bruno Vellas[4,5,6] | Sandrine Andrieu[5,6,7] | Nicola Coley[5,6,7] | Tiia Ngandu[8] | MAPT/DSA group*

Alzheimer's Dement. 2022;1–11.

1680 non demented « frail » older adults

- Memory complaint; Limitation in one instrumental activity; Slow gait

Four intervention arms

- Multidomain + omega3
- Muliidomain + placebo
- Omega3
- Placebo

Multidomain

- Memory training (MEMO- Belleville et al)
- Reasoning training (Active- Willis et al)
- Physical activity guidelines
- Nutrition guidelines

Assessment

- 6, 12, 24 36 months

PARTICIPANTS

749 in the multidomain arms

DOSE

Number of cognitive training sessions attended (1-28)

INDIVIDUAL FACTORS

Education

Level of frailty

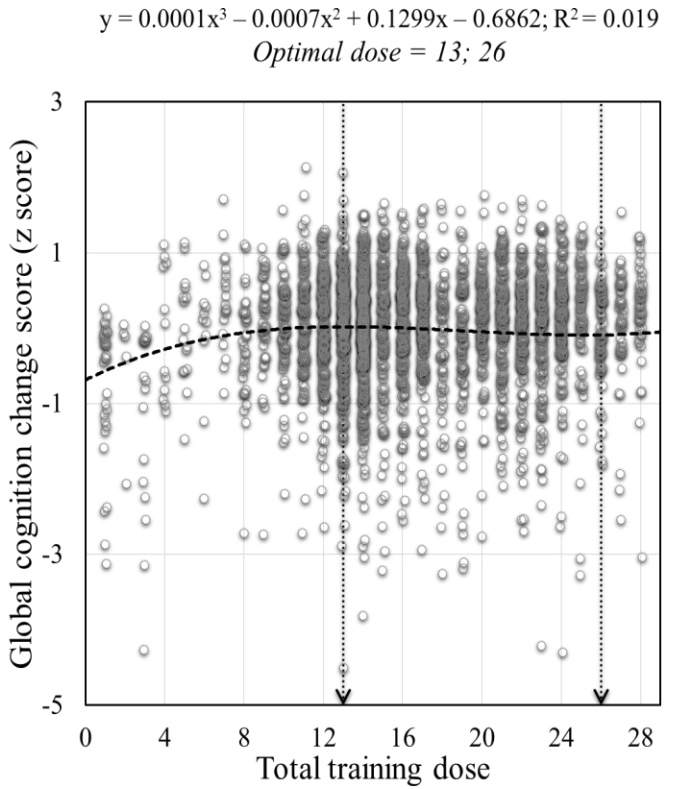
Age

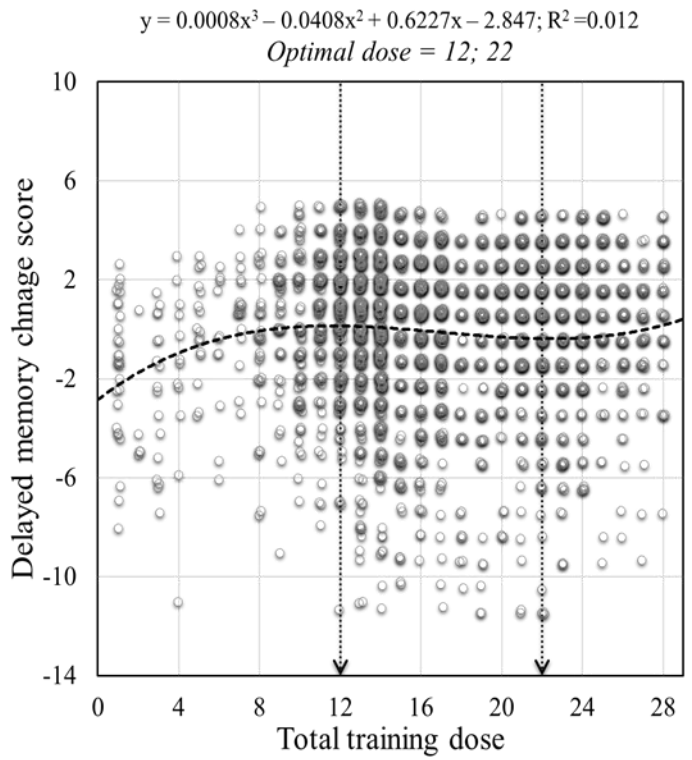
Vascular risk with CAIDE score

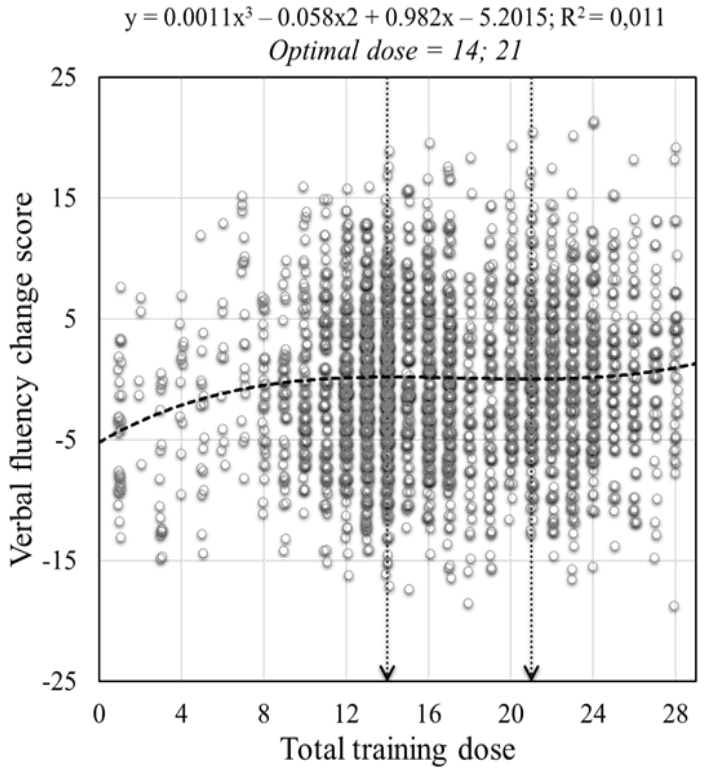
ApoE4

Sex

A RAPID INCREASE WITH OPTIMAL DOSE AT 12-14 SESSIONS FOLLOWED BY A LONG PLATEAU







1. Polynomial regression to determine best model to fit cognition over time.
2. Residuals Expected vs raw scores at each time.
3. Mixed-model analysis to assess the effect of the dose on these residuals
4. Optimal dose: first critical point in the polynomial.

FUNCTIONAL NEUROIMAGING

Understand the **mechanism** by which training exerts its effects:

- **Strategy training**
  - Activation in regions that are not typically involved in the task (new activation) and in regions that are consistent with the type of strategies provided (e.g.: imagery: parietal lobe).
- **Process-based training**
  - Changes in the region typically involved in the task.

STRATEGY TRAINING RELATED BRAIN CHANGES

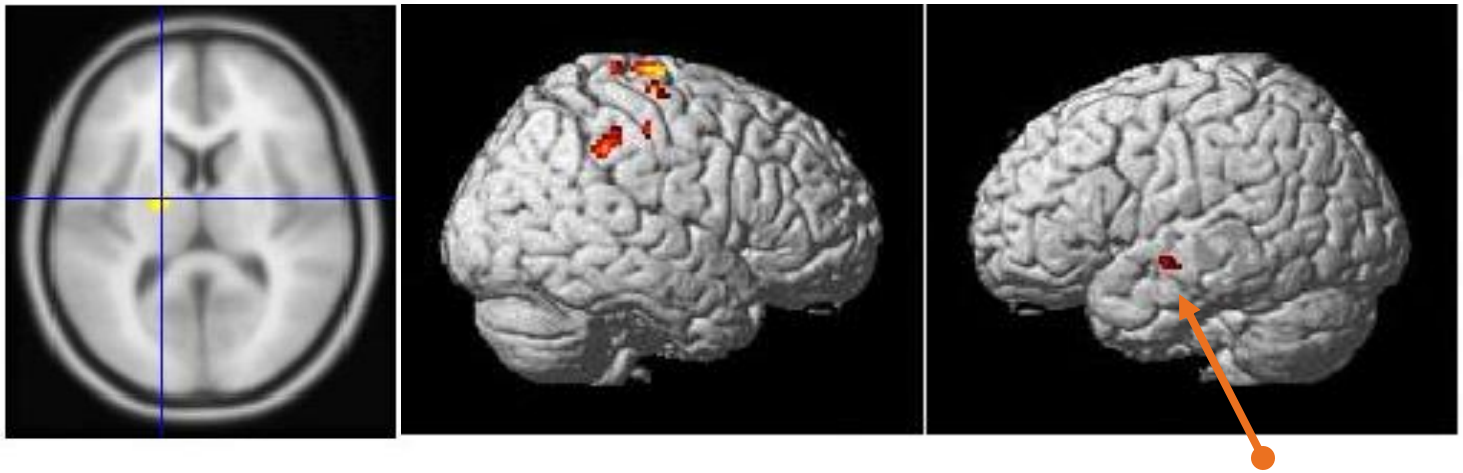
BRAIN
A JOURNAL OF NEUROLOGY
Brain 2011: 134; 1623–1634

Training-related brain plasticity in subjects at risk of developing Alzheimer's disease

Sylvie Belleville,[1] Francis Clément,[1] Samira Mellah,[1] Brigitte Gilbert,[2] Francine Fontaine[2] and Serge Gauthier[3]

Programme d'intervention cognitive pour les aînés MEMO

Encoding post>pre2 (word-nonword)



New New Increased

Activation of new regions involved in the mnemonic learned

ACTIVATION OF NEW REGIONS

Left thalamus, putamen and globus pallidus
Right inferior parietal lobule
Right superior frontal gyrus
Right cerebellum

INCREASED ACTIVATION

Left superior temporal gyrus and insula (13,21,22)

STRATEGIC VS PROCESS-BASED TRAINING IN DUAL-TASK

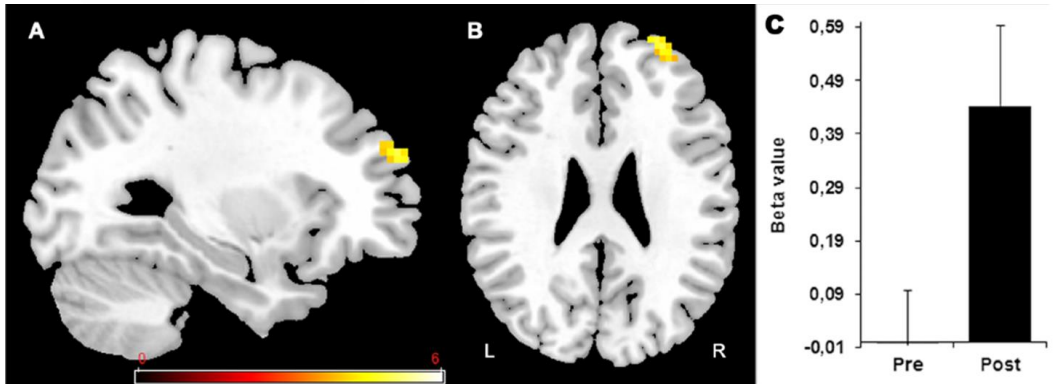
OPEN ACCESS Freely available online PLOS ONE

The Pattern and Loci of Training-Induced Brain Changes in Healthy Older Adults Are Predicted by the Nature of the Intervention

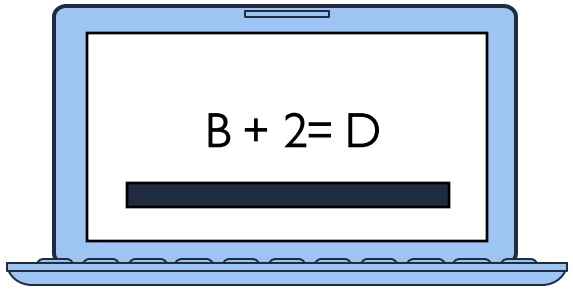
Sylvie Belleville[1,2*], Samira Mellah[1], Chloé de Boysson[1], Jean-Francois Demonet[3], Bianca Bier[1,2]

August 2014 | Volume 9 | Issue 8 | e102710

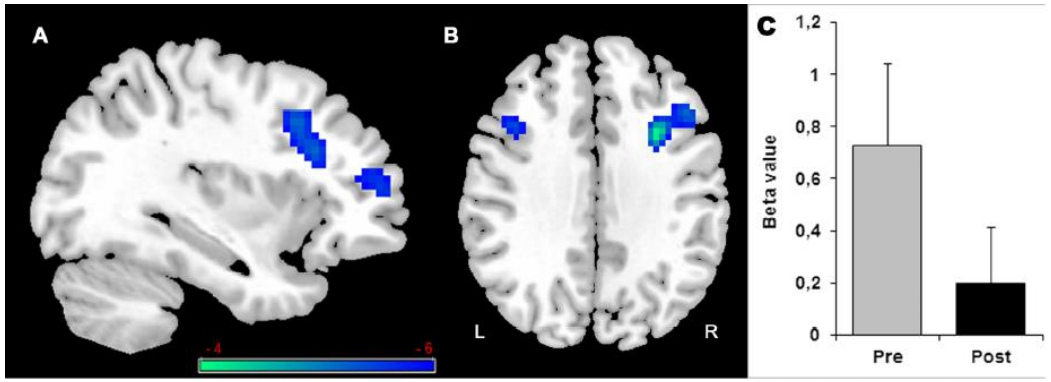
VARIABLE PRIORITY TRAINING



New post-training activation (Post > Pre) in prefrontal area 10, when dual-tasking
(multitasking control)



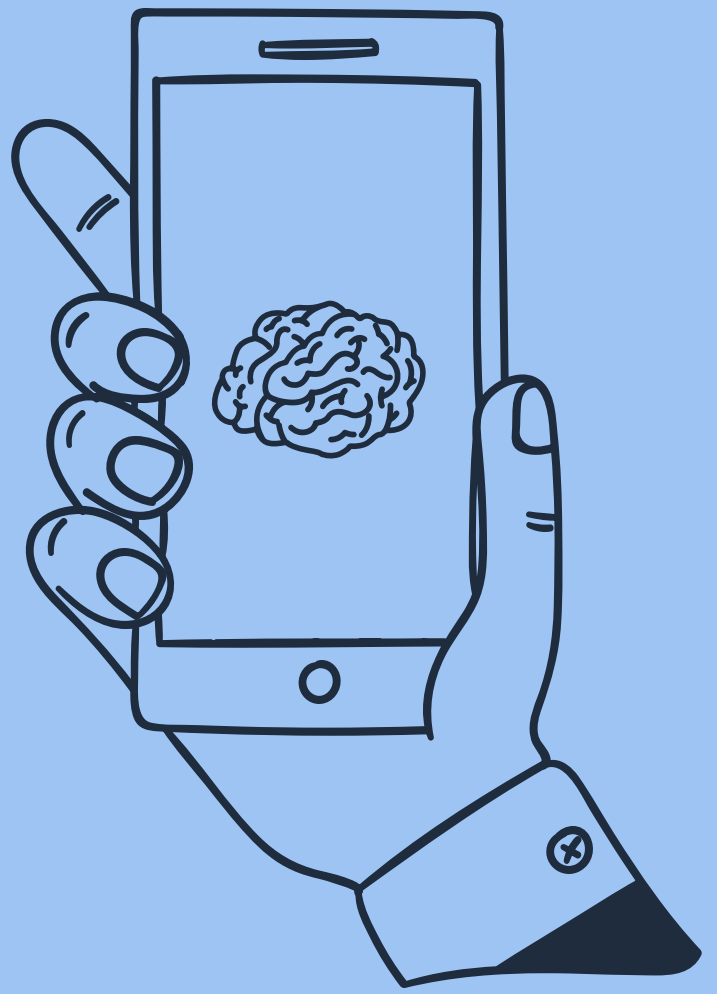
REPEATED PRACTICE



Reduced activation (Pre>Post) in inferior and middle frontal gyri bilaterally and in the left thalamus when single-tasking
(working memory)

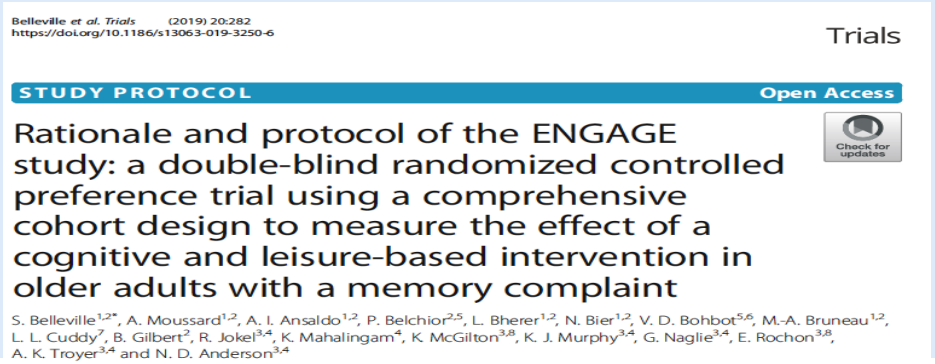
BRINGING INTERVENTION TO THE REAL WORLD

Increase relevance and engagement



Adapt cognitive training to virtual reality

LEISURE ACTIVITIES OFFER MULTIPLE OPPORTUNITIES OF ENRICHMENT


Belleville et al. Trials (2019) 20:282
https://doi.org/10.1186/s13063-019-3250-6

Trials

STUDY PROTOCOL Open Access

Rationale and protocol of the ENGAGE study: a double-blind randomized controlled preference trial using a comprehensive cohort design to measure the effect of a cognitive and leisure-based intervention in older adults with a memory complaint

S. Belleville[1,2*], A. Moussard[1,2], A. I. Ansaldo[1,2], P. Belchior[2,5], L. Bherer[1,2], N. Bier[1,2], V. D. Bohbot[5,6], M.-A. Bruneau[1,2], L. L. Cuddy[7], B. Gilbert[2], R. Jokel[3,4], K. Mahalingam[4], K. McGilton[3,8], K. J. Murphy[3,4], G. Naglie[3,4], E. Rochon[3,8], A. K. Troyer[3,4] and N. D. Anderson[3,4]

ENGAGE: A COMMUNITY-BASED LEISURE + COGNITIVE TRAINING INTERVENTION

A 2-year multisite 2-arm trial financed by CCNA (CIHR) in 144 older adults with SCD or MCI

Combine formal training with leisure activities known to be neuroprotective: **Music** and **spanish learning**

To make the intervention more **enjoyable and engaging** to older adults from different background.

CCNA Team 10

CCNA CCNV
Canadian Consortium on Neurodegeneration in Aging
Consortium Canadien en neurodégénérescence associée au Vieillissement

APPLYING IMPLEMENTATION SCIENCE TO COGNITIVE TRAINING

Main barriers to implementing cognitive interventions in clinics (Pike et al, 2024)

1. Organizational (financial, human resources and space)

- Activities to create buy-in from the managers who provide resources.

2. Training content not flexible enough

- Balance between standardized interventions and keeping flexibility to adapt them to different contexts of practice.

3. Needs for expertise development

- training and support to therapists to maintain their sense of competence.

Pike KE, Li L, Naismith SL, Bahar-Fuchs A, Lee A, Mehrani I, et al. Implementation of Cognitive (Neuropsychological) Interventions for Older Adults in Clinical or Community Settings: A Scoping Review. *Neuropsychol Rev* 2024

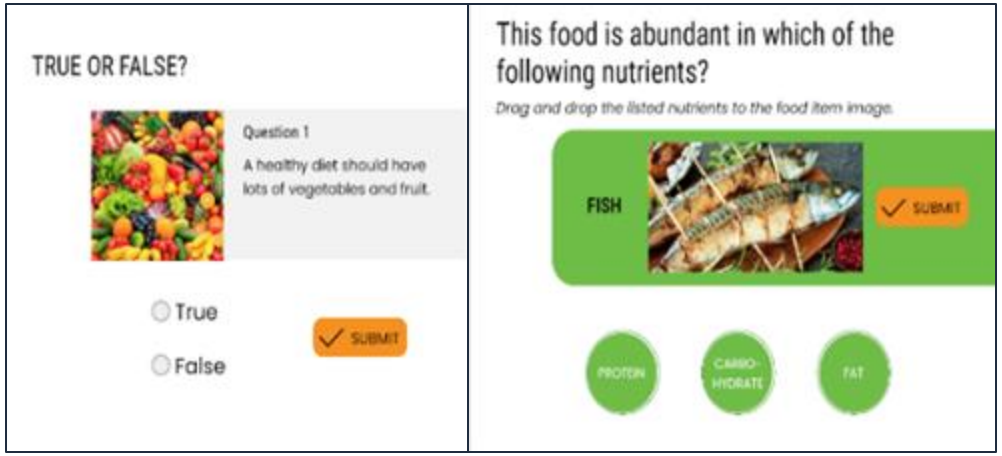
Using online platform Brain Health PRO

PI for CTU: H. Feldman, S. Belleville, H. Chertkow, M. Montero-Odesso, H. Nygaard
PI for Implementation: S. Belleville, N. Anderson, N. BenGaied, I. Itzhak, E. Kroger, W. Wittich

An online educational program focusing on **7 modifiable risk factors for dementia**

181 short animated chapters (4 chapters per week over 10 months)

Implementation with group supports/social activities within the Quebec Alzheimer Federation local chapters.



IMPLEMENTATION OF GROUP SUPPORT WITH LOCAL ALZHEIMER'S ASSOCIATION

The program

BARRIERS

-Not adapted enough to individual's need and level: too easy for some, too difficult for others.

-Repetitive; too long.

ENABLERS

-The technical support.

The social activities

BARRIERS

-Inconsistent participation.

-Transportation issues in rural and urban areas.

ENABLERS

-Judged as critically important.

-Possibility to attend in-person and virtual groups.

The organisation

BARRIERS

-Lack of control on schedule.

-Human resources (trained staff leaving during the program).

ENABLERS

-More training and mentoring for facilitators.

-More people trained.

CONCLUSION

- STRATEGY TRAINING DOES IMPROVE COGNITION IN A POTENTIALLY DURABLE WAY AND SOME TRANSFER IS OBSERVED.
- DOSE-RESPONSE IS MOSTLY NON-LINEAR : RAPID EFFECT WITH VERY SLOW FURTHER IMPROVEMENT.
  - MORE DOSE IS NOT ALWAYS BETTER BUT SOME PEOPLE BENEFIT FROM MORE.
- NEUROIMAGING CONTRIBUTES TO MECHANISTIC MODELS OF TRAINING AND RESERVE.
- WE NOW NEED TO BETTER ADDRESS ACCESS, IMPLEMENTATION AND UPSCALING.

Professionals
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Mohamed Abdelhaf Kardi
David Predovan
Jeff Ferreri
Aline Moussard
Marc Cuesta
Asma Fadhlaoui
Amal Trigui
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Haakon Niigard

THANK YOU

Supporting agencies

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