Strategies for Cognitive Impairment:

*Non-Pharmacological Behavioral Interventions*

Jose A. Muñoz-Moreno, Ph.D

Lluita contra la SIDA Foundation
Germans Trias i Pujol University Hospital
Barcelona, Catalonia, Spain
Disclosure

Dr. Jose A. Muñoz-Moreno

October 2016

• Dr. Muñoz-Moreno has received **research funding** from AbbVie and ViiV Healthcare.

• Dr. Muñoz-Moreno has received **speaker honoraria** from Gilead Sciences, Merck Sharp & Dohme, and ViiV Healthcare.

• Dr. Muñoz-Moreno has received **consulting fees** from AlbaJuna Therapeutics, SL.
1. To point out potential effective non-pharmacological behavioral strategies for HIV-related cognitive impairment, from a clinical perspective.

2. To show the effectiveness and characteristics of those interventions.
Comprehensive Approach

Cognitive Impairment

Pharmacological

1. CNS efficacy
2. Time initiation
3. ARV-related management

Non-Pharmacological

1. Antidepressant
2. Antibiotics
3. Mood stabilizers

ARV-Related

1. Brain fitness
2. Compensatory strategies
3. Cognitive remediation

Adjuvant

1. Physical exercise
2. Nutrition changes
3. Sleep hygiene

Cognitive Stimulation

Behavioral

...
Comprehensive Approach

Cognitive Impairment

Pharmacological

Non-Pharmacological

ARV-Related

Adjuvant

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3. Sleep hygiene

Jose A. Muñoz-Moreno / Oct 2016 / Toronto
Behavioral Interventions for Cognitive Impairment
1. Psychotherapeutic Approach:
   • Cognitive Behavioral Therapy
   • Other

2. Mindfulness / Meditation Techniques

3. Other Lifestyle Interventions:
   • Nutrition
   • Sleep Hygiene
1. Cognitive Behavioral Therapy
Psychotherapeutic Approach

- Cognitive Behavioral Therapy
- Systemic Family Therapy
- Psychodynamic Therapy
- Acceptance and Commitment Therapy
- Humanistic Therapy

- Counseling + Psychoeducation
- Group Therapy
Psychotherapeutic Approach

- To increase motivation to change.
- To reduce anxiety and distressing thoughts.
- To learn to manage emotions by oneself.
- To reduce life stressors.
- To establish and enhance commitments in life.
Psychotherapeutic Approach

- Self-monitoring
- Bibliotherapy
- Environmental restructuring
- Parenting skills development
- Pleasant activity scheduling
- Problem-solving skills development
- Relaxation
- Systematic desensitization
- Cognitive restructuring
- Homework
- Planning
- Positive self-talk
- Self-instruction
- Cognitive rehearsal
- Behavioral rehearsal
- In vivo exposure
- Exposure and response prevention
Cognitive Behavioral Therapy (CBT)
Cognitive Behavioral Therapy (CBT)

fMRI Activation During Executive Function Predicts Response to Cognitive Behavioral Therapy in Older, Depressed Adults

Dolores Gallagher Thompson, Ph.D., Shelli R. Kesler, Ph.D., Keith Sudheimer, Ph.D., Kala Mebenda Mehta, D.Sc., Larry W. Thompson, Ph.D., Renee M. Marquett, Ph.D., M.B.A., Jason M. Holland, Ph.D., Robert Reiser, Ph.D., Natalie Rasgon, M.D., Alan Schatzberg, M.D., Ruth M. O’Hara, Ph.D.

Thompson et al, Am J Geriatr Psychiatry, 2014
fMRI Activation During Executive Function Predicts Response to Cognitive Behavioral Therapy in Older, Depressed Adults

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Natalie Rasgon, M.D., Alan Schatzberg, M.D., Ruth M. O’Hara, Ph.D.

Task (WCST) was the primary predictor variable. Results: 67% of patients had a positive response to CBT. Decreased activation in the left inferior frontal triangle and right superior frontal gyrus as well as increased activity in the right middle frontal gyrus and left superior frontal gyrus predicted a positive response to CBT. Demographic and neu-
Resting-state connectivity of the amygdala predicts response to cognitive behavioral therapy in obsessive compulsive disorder

Martin Göttlich\(^a,\)\(^*,\) Ulrike M. Krämer\(^a,\)\(^d,\) Andreas Kordon\(^b,\) Fritz Hohagen \(^b,\) Bartosz Zurowski\(^b,\)\(^c\)

\(^a\) Department of Neurology, University of Lübeck, Lübeck, Germany
\(^b\) Department of Psychiatry, University of Lübeck, Lübeck, Germany
\(^c\) University of Hamburg, Institute for Systems Neuroscience, Germany
\(^d\) Institute for Psychology II, University of Lübeck, Lübeck, Germany

Göttlich et al., Biological Psychology, 2015
Cognitive Behavioural Therapy (CBT)

Cognitive behavioural therapy for adherence and depression in patients with HIV: a three-arm randomised controlled trial

Steven A Safren, C Andres Bedoya, Conall O’Cleirigh, Katie B Biello, Megan M Pinkston, Michael D Stein, Lara Traeger, Erna Kojic, Gregory K Robbins, Jonathan A Lerner, Debra S Herman, Matthew J Mimiaga, Kenneth H Mayer

Safren et al, Lancet, Sept 2016
Cognitive Behavioural Therapy (CBT)

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Safren et al, Lancet, Sept 2016

| Table 2: Adjusted acute outcome scores (at 4 month follow-up assessment) by study condition |
|----------------------------------|----------------|---------------|------------------|----------------|
|                                  | CBT-AD         | Comparison intervention | b (95% CI)* | p value   |
| ETAU as comparison               |                |                            |               |           |
| CGI score                         | 2.60 (0.13)    | 3.26 (0.18)               | -0.66 (-1.11 to -0.21) | 0.005     |
| MADRS score                       | 17.65 (1.03)   | 22.33 (1.38)              | -4.69 (-8.09 to -1.28) | 0.007     |
| CD4 count (cells per μL)          | 586.86 (19.68) | 595.55 (26.45)            | -8.69 (-73.31 to 55.92) | 0.791     |
| Viral load (log₁₀ copies per mL)  | 1.99 (0.06)    | 2.10 (0.08)               | -0.11 (-0.31 to 0.09)  | 0.288     |
| Detectable viral load, proportion | 0.17 (0.06)    | 0.17 (0.04)               | 0.13 (-0.91 to 1.18)   | 0.799     |
| ISP-AD as comparison              |                |                            |               |           |
| CGI score                         | 2.60 (0.14)    | 2.80 (0.13)               | -0.20 (-0.58 to 0.19)  | 0.308     |
| MADRS score                       | 18.48 (1.03)   | 19.04 (1.00)              | -0.56 (-3.43 to 2.30)  | 0.698     |
| CD4 count (cells per μL)          | 593.73 (21.42) | 603.42 (21.21)            | -9.69 (-69.16 to 49.78) | 0.748     |
| Viral load (log₁₀ copies per mL)  | 1.98 (0.06)    | 2.09 (0.06)               | -0.11 (-0.27 to 0.06)  | 0.211     |
| Detectable viral load, proportion | 0.16 (0.04)    | 0.20 (0.05)               | -0.31 (-1.15 to 0.53)  | 0.471     |
Cognitive behavioural therapy for adherence and depression in patients with HIV: a three-arm randomised controlled trial

Steven A Safren, C Andres Bedoya, Conall O’Cleirigh, Katie B Biello, Megan M Pinkston, Michael D Stein, Lara Traeger, Erna Kojic, Gregory K Robbins, Jonathan A Lerner, Debra S Herman, Matthew J Mimiaga, Kenneth H Mayer

Safren et al, Lancet, Sept 2016
Cognitive Behavioral Therapy (CBT)

Internet-Delivered Cognitive Behavioural Therapy for Adults with Mild to Moderate Depression and High Cardiovascular Disease Risks: A Randomised Attention-Controlled Trial

Nicholas Glozier¹*, Helen Christensen², Sharon Naismith¹, Nicole Cockayne¹, Liesje Donkin¹, Bruce Neal³, Andrew Mackinnon⁴, Ian Hickie¹

Glozier et al, PLOS One, 2013

| Table 4. Baseline to post-intervention change under iCBT (E-couch) and control (HealthWatch) on depression, adherence, anxiety, disability and activity measures. |
|---|---|---|---|---|
| **Outcome** | **Baseline–post intervention change** | **Interaction** | |
| | **Active (E-couch)** | **Control (HealthWatch)** | **Difference** | **Test** |
| Depression (PHQ-9) | 3.66 (3.05–4.27) | 2.60 (2.05–3.16) | 1.06 (0.23–1.89) | P = .01 |
| Adherence (MOS Patient Adherence Scale Specific) | 2.72 (1.35–4.09) | 0.56 (–0.65–1.77) | 2.16 (0.33–3.99) | P = .02 |
| Anxiety (GAD7) | 2.44 (1.87–3.02) | 1.48 (0.97–1.99) | 0.96 (0.19–1.73) | P = .01 |
| Disability - WHODAS II total score | 1.08 (0.55–1.61) | 0.68 (0.22–1.44) | 0.40 (–0.30–1.10) | P = .26 |

All contrasts are scaled so that a positive value indicates improvement.
Contrast value (95% Confidence Interval). doi:10.1371/journal.pone.0059139.t004

Jose A. Muñoz-Moreno / Oct 2016 / Toronto
Behavioral Interventions for Cognitive Impairment
2. Mindfulness / Meditation Techniques
Mindfulness / Meditation Techniques

Mindfulness

Strive to focus on the present
Mindfulness / Meditation Techniques

• Mental Health Disorders:
  Depression, Anxiety Disorders, Addictions, and Psychosis

• Medical Disorders:
  Chronic Pain and Cancer

3 psychological / neurobiological mechanisms:

1) Attention control
2) Emotional regulation
3) Self-awareness changes

Hervás et al, Clínica y Salud, 2016
The neuroscience of mindfulness meditation

Yi-Yuan Tang1,2*, Britta K. Hölzel3,4* and Michael I. Posner2


Figure 1 | Brain regions involved in the components of mindfulness meditation. Schematic view of some of the brain regions involved in attention control (the anterior cingulate cortex and the striatum), emotion regulation (multiple prefrontal regions, limbic regions and the striatum) and self-awareness (the insula, medial prefrontal cortex and posterior cingulate cortex and precuneus).
Mindfulness / Meditation Techniques
Mindfulness / Meditation Techniques

Search results
Items: 4

1. [Review of the effects of mindfulness meditation on mental and physical health and its mechanisms of action].
   Ngô TL.
   PMID: 24719001
   Similar articles

2. Effectiveness of Mindfulness-Based Cognitive Therapy on the Quality of Life, Emotional Status, and CD4 Cell Count of Patients Aging with HIV Infection.
   AIDS Behav. 2013 Sep 28. [Epub ahead of print]
   PMID: 24077971
   Similar articles

3. Mindfulness-based interventions for physical conditions: a narrative review evaluating levels of evidence.
   Carlson LE.
   PMID: 23762768 Free PMC Article
   Similar articles

   Amaro H, Magno-Gatmaytan C, Meléndez M, Cortés DE, Arevalo S, Margolin A.
   PMID: 20408063
   Similar articles
Mindfulness / Meditation Techniques

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Items: 4

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Behavioral Interventions for Cognitive Impairment
Mindfulness / Meditation Techniques

Effectiveness of Mindfulness-Based Cognitive Therapy on the Quality of Life, Emotional Status, and CD4 Cell Count of Patients Aging with HIV Infection

Marian Gonzalez-García · Maria Jose Ferrer · Xavier Borras · Jose A. Muñoz-Moreno · Cristina Miranda · Jordi Puig · Nuria Perez-Alvarez · Joaquim Soler · Albert Fellu-Soler · Bonaventura Clotet · Carmina R. Fumaz

González-García et al, AIDS Behav, 2013
Mindfulness / Meditation Techniques

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Table 2: Evolution of study variables during follow-up

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>Week 8</th>
<th>Week 20</th>
<th>Statistics</th>
<th>d</th>
<th>Statistics</th>
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<tbody>
<tr>
<td></td>
<td>MBCT</td>
<td>Control</td>
<td>MBCT</td>
<td>Control</td>
<td>p</td>
<td>MBCT</td>
</tr>
<tr>
<td></td>
<td>(n = 19)</td>
<td>(n = 20)</td>
<td>(n = 19)</td>
<td>(n = 20)</td>
<td></td>
<td>(n = 15)</td>
</tr>
<tr>
<td>NHP-total</td>
<td>47.5 (22.8)</td>
<td>44.9 (26.3)</td>
<td>19.8 (18)</td>
<td>43.1 (27.1)</td>
<td>-3.3170</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>NHP-energy</td>
<td>65.2 (47.5)</td>
<td>67.6 (40.9)</td>
<td>28.2 (37.2)</td>
<td>61.8 (42.5)</td>
<td>-2.6170</td>
<td>.01</td>
</tr>
<tr>
<td>NHP-pain</td>
<td>47.5 (38.4)</td>
<td>42.4 (36.3)</td>
<td>21.3 (26.4)</td>
<td>35.5 (35.2)</td>
<td>-1.8010</td>
<td>.04</td>
</tr>
<tr>
<td>NHP-emotional</td>
<td>56.4 (30.8)</td>
<td>47.3 (34.1)</td>
<td>13 (20)</td>
<td>48.4 (39.5)</td>
<td>-3.5550</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>NHP-sleep</td>
<td>49.5 (35.9)</td>
<td>52.5 (34.9)</td>
<td>28.6 (33.3)</td>
<td>49.6 (33.4)</td>
<td>-1.9420</td>
<td>.30</td>
</tr>
<tr>
<td>NHP-social isolation</td>
<td>44.8 (30.9)</td>
<td>38.7 (27.8)</td>
<td>13.6 (18.6)</td>
<td>37.7 (30.4)</td>
<td>-3.0050</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>NHP-mobility</td>
<td>25.5 (19.6)</td>
<td>20.9 (16)</td>
<td>16.8 (12.9)</td>
<td>24 (17.6)</td>
<td>-2.4340</td>
<td>.01</td>
</tr>
<tr>
<td>PSS-10</td>
<td>24.1 (5.7)</td>
<td>21.5 (6.5)</td>
<td>13.4 (7.4)</td>
<td>21 (5.1)</td>
<td>-3.7260</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>BDI-II</td>
<td>25.1 (12.4)</td>
<td>21.3 (12.6)</td>
<td>10.1 (9.3)</td>
<td>19.9 (13.9)</td>
<td>-3.7330</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>BAI</td>
<td>26.5 (12)</td>
<td>21.5 (10.3)</td>
<td>14.4 (13.1)</td>
<td>19.8 (11.2)</td>
<td>-2.9200</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>CD4 cell count, cells/mL²</td>
<td>555 (198)</td>
<td>493 (223)</td>
<td>614 (185)</td>
<td>516 (238)</td>
<td>-1.3670</td>
<td>.09</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD), p value and d = effect size

NHP Nottingham Health Profile, PSS Perceived Stress Scale, BDI Beck Depression Inventory, BAI Beck Anxiety Inventory

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Behavioral Interventions for Cognitive Impairment
Mindfulness / Meditation Techniques

Effectiveness of Mindfulness-Based Cognitive Therapy on the Quality of Life, Emotional Status, and CD4 Cell Count of Patients Aging with HIV Infection

Marian Gonzalez-Garcia · Maria Jose Ferrer · Xavier Borras · Jose A. Munoz-Moreno · Cristina Miranda · Jordi Puig · Nuria Perez-Alvarez · Joaquim Soler · Albert Feliu-Soler · Bonaventura Clotet · Carmina R. Fumaz

Fig. 3 Severity of depressive symptoms in MBCT group during follow-up according to BDI-II scores

Wk 8:  \( p=0.09 \)

Wk 20:  \( p<0.001 \)
Mindfulness / Meditation Techniques

The Effects of Mindfulness on Persons with Mild Cognitive Impairment: Protocol for a Mixed-Methods Longitudinal Study

Wong et al, Frontiers in Aging Neuroscience, Jun 2016
Mindfulness / Meditation Techniques

FIGURE 1 | Stages of study protocol. Abbreviations (in alphabetical order): B-ADL, Bayer Activities of Daily Living (25-item); DASS 21, Depression Anxiety Stress Scales (21-item); DHL, Demographic, Health and Lifestyle questionnaire; FMI, Freiburg Mindfulness Inventory (14-item); MAQ, Mindfulness Adherence Questionnaire (12-item); MCI, Mild Cognitive Impairment; MoCA, Montreal Cognitive Assessment.

Wong et al, Frontiers in Aging Neuroscience, Jun 2016
3. Lifestyle Interventions
# Conceptual Approach

<table>
<thead>
<tr>
<th>Related to HOST</th>
<th>Related to INFECTION</th>
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<tbody>
<tr>
<td><strong>Demographic/psychosocial</strong></td>
<td><strong>Comorbidities</strong></td>
</tr>
<tr>
<td>Older age</td>
<td>HCV coinfection</td>
</tr>
<tr>
<td>Low education level / illiteracy</td>
<td>Drug use</td>
</tr>
<tr>
<td>Low socioeconomic status</td>
<td>CDV risk factors</td>
</tr>
<tr>
<td>Unemployed</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Risk behaviors</td>
<td>Psychiatric disorder</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

**Jose A. Muñoz-Moreno / Oct 2016 / Toronto**

*Behavioral Interventions for Cognitive Impairment*
# Conceptual Approach

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Jose A. Muñoz-Moreno / Oct 2016 / Toronto
Behavioral Interventions for Cognitive Impairment
## Conceptual Approach

<table>
<thead>
<tr>
<th>Demographic/psychosocial</th>
<th>Comorbidities</th>
<th>HIV</th>
<th>ART Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>HCV coinfection</td>
<td>AIDS</td>
<td>Poor adherence</td>
</tr>
<tr>
<td>Low education level /illiteracy</td>
<td>Drug use</td>
<td>Low nadir CD4+</td>
<td>ART interruption</td>
</tr>
<tr>
<td>Low socioeconomic status</td>
<td>CDV risk factors</td>
<td>Highest viral load</td>
<td>Late ART initiation</td>
</tr>
<tr>
<td>Unemployed</td>
<td>Diabetes</td>
<td>HIV clade (A, B)</td>
<td>ARV neurotoxicity</td>
</tr>
<tr>
<td>Risk behaviors</td>
<td>Psychiatric disorder</td>
<td>Tropism (dual-mixed, env n283)</td>
<td>IRIS</td>
</tr>
</tbody>
</table>

... ... ... ...
Nutrition

Mediterranean Diet and Age-Related Cognitive Decline
A Randomized Clinical Trial

Cinta Valls-Pedret, MSc; Aleix Sala-Vila, DPharm, PhD; Mercè Serra-Mir, RD; Dolores Corella, DPharm, PhD; Rafael de la Torre, DPharm, PhD; Miguel Ángel Martínez-González, MD, PhD; Elena H. Martínez-Lapiscina, MD, PhD; Montserrat Fitó, MD, PhD; Ana Pérez-Heras, RD; Jordi Salas-Salvadó, MD, PhD; Ramon Estruch, MD, PhD; Emilio Ros, MD, PhD

Valls-Pedret et al, JAMA Intern Med, 2015

Cognitive enhancement by omega-3 fatty acids from child-hood to old age: Findings from animal and clinical studies

Dirk W. Luchman, Cai Song

Luchman et al, Neuropharmacology, 2013

- n=447 participants
- 52% women
- 6-year follow-up
- Frontal + global cognition
- Mediterranean diet: olive oils + nuts
- Review
- Animal + clinical
- Omega-3 acids
Sleep Hygiene

---

**Pills or Push-Ups? Effectiveness and Public Perception of Pharmacological and Non-Pharmacological Cognitive Enhancement**

Lucius Caviola* and Nadira S. Faber†,*

Department of Experimental Psychology, University of Oxford, Oxford, UK; Department of Clinical Psychology, University of Oxford, Oxford, UK

---

Caviola and Faber, Frontiers in Psychology, Dec 2015
Sleep Hygiene

1) The reviewed evidence suggests that computer training, physical exercise, and sleep can moderately enhance cognitive functions.

2) Benefits by NPCI techniques present similar effect sizes than current PCI strategies.

Caviola and Faber, Frontiers in Psychology, Dec 2015
Understanding and optimizing brain health in HIV now: protocol for a longitudinal cohort study with multiple randomized controlled trials

Nancy E. Mayo¹,², Marie-Josée Brouillette³, Lesley K. Fellows⁴* and Positive Brain Health Now Investigators

Mayo et al, BMC Neurology, Jun 2016
## Table 3: Planned pilot trials for the brain health now study

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Site</th>
<th>Selection criteria [outcome measure]</th>
<th>Other criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive training</td>
<td>Montreal</td>
<td>B-CAM level including a self-report cognitive concern [B-CAM primary/secondary]</td>
<td>Other criterion</td>
</tr>
<tr>
<td>Insomnia intervention</td>
<td>All</td>
<td>(Primary)</td>
<td>Sleep dissatisfaction</td>
</tr>
<tr>
<td>Exercise</td>
<td>Montreal</td>
<td>(Primary)</td>
<td>Sedentary; physical function limitations</td>
</tr>
<tr>
<td>Sleep apnea intervention</td>
<td>Selected</td>
<td>(Primary)</td>
<td>Sleep dissatisfaction / sleep apnea screen</td>
</tr>
<tr>
<td>Goal management training</td>
<td>Selected</td>
<td>(Primary)</td>
<td>Depressive symptoms</td>
</tr>
<tr>
<td>Cognitive behavioural therapy</td>
<td>Montreal</td>
<td>(Secondary)</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Relaxation</td>
<td>Montreal</td>
<td>(Secondary)</td>
<td></td>
</tr>
</tbody>
</table>

Indicates that selection criteria include a score lower than the mean on the B-CAM

---

*Mayo et al, BMC Neurology, Jun 2016*
1. There are several behavioral strategies that potentially can help to improve cognitive impairment in people with HIV.

2. Those strategies include psychotherapies, counseling/supportive care, and intervention on lifestyle factors.

3. More research is required for HIV population, providing data on both applicability and effectiveness.
4. For the moment we can learn from the investigation done in other health areas.

4. We can also use the vast evidence in HIV infection about risk and protective factors for cognitive impairment in order to intervene.

5. A healthy lifestyle is always the final goal, since benefits for the body and mind are always benefits for the brain.
Thanks!

Jose A. Muñoz-Moreno, Ph.D.

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