



Music and Alzheimer's Disease: New Insights

Dr. Corinne Fischer

**Co-Director, St. Michael's hospital Memory Clinic,
Associate Professor, Department of Psychiatry,
University of Toronto**

St. Michael's

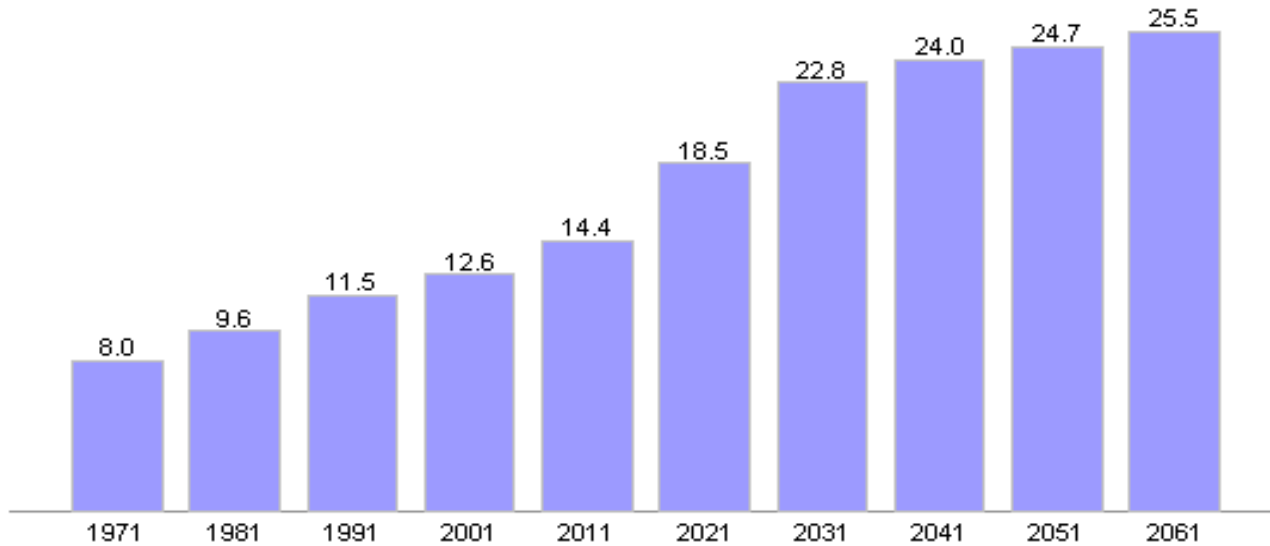
Inspired Care. Inspiring Science.

Objectives

- To briefly review our understanding of AD and related treatments
- To review the existing literature on music and Alzheimer's disease
- To discuss a recent study where we examined the effect of music exposure on brain activity in patients with AD
- To discuss future treatment applications



**Population 65 years and over, Canada, Historical (1971-2011) and Projected (2012-2061)
(percent)**



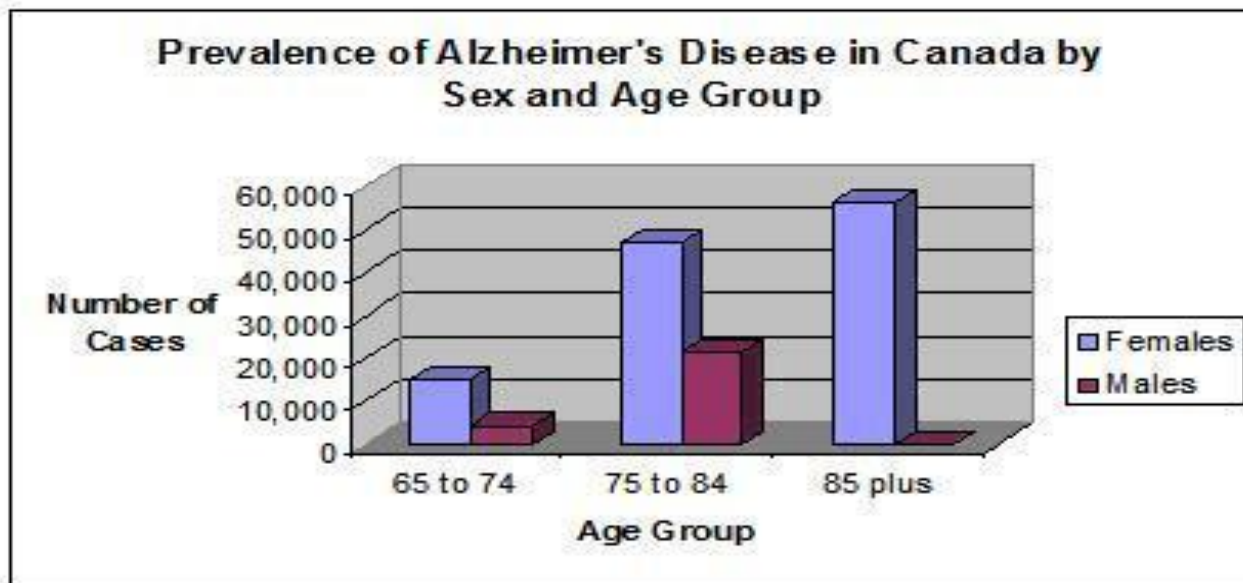


Figure 2: AD by Sex and Age [3]



What is Alzheimer's disease



- A neurodegenerative disorder that involves the accumulation of amyloid plaques and tangles
- Clinically associated with progressive declines in memory and cognitive functioning
- No cure though current treatments are modestly effective (Lanctot et al 2002)



Healthy
Brain

Severe
Alzheimer's

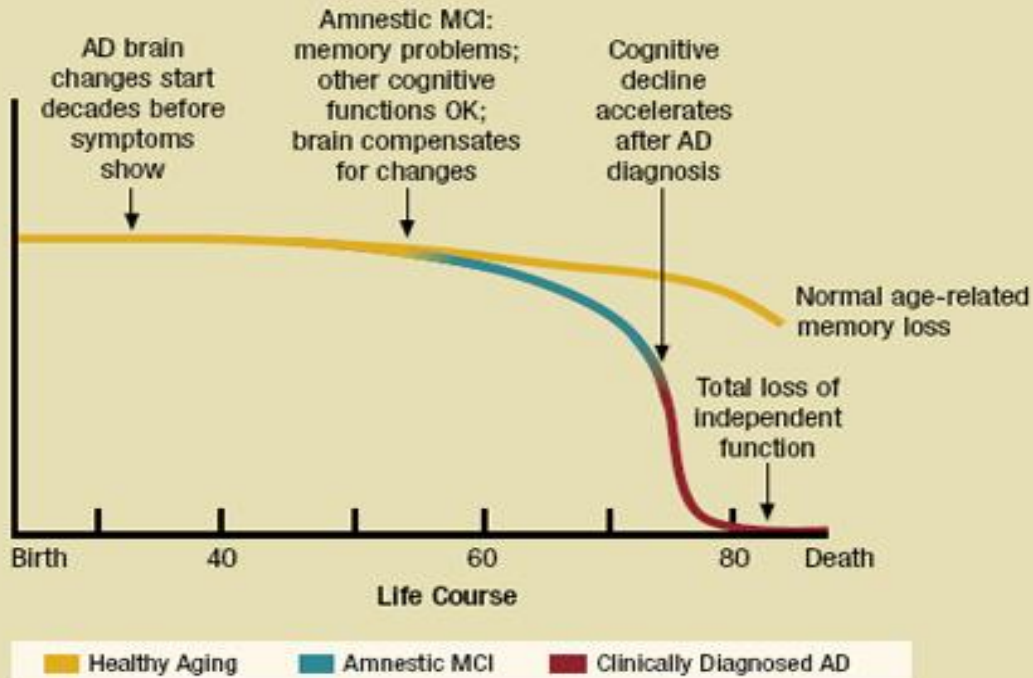


Recent advances in our understanding

- Amyloid starts to accumulate in the AD brain many years before clinical disease expression
- Clinical symptoms do not always reflect pathology
- Other pathologies may contribute equally to clinical disease expression



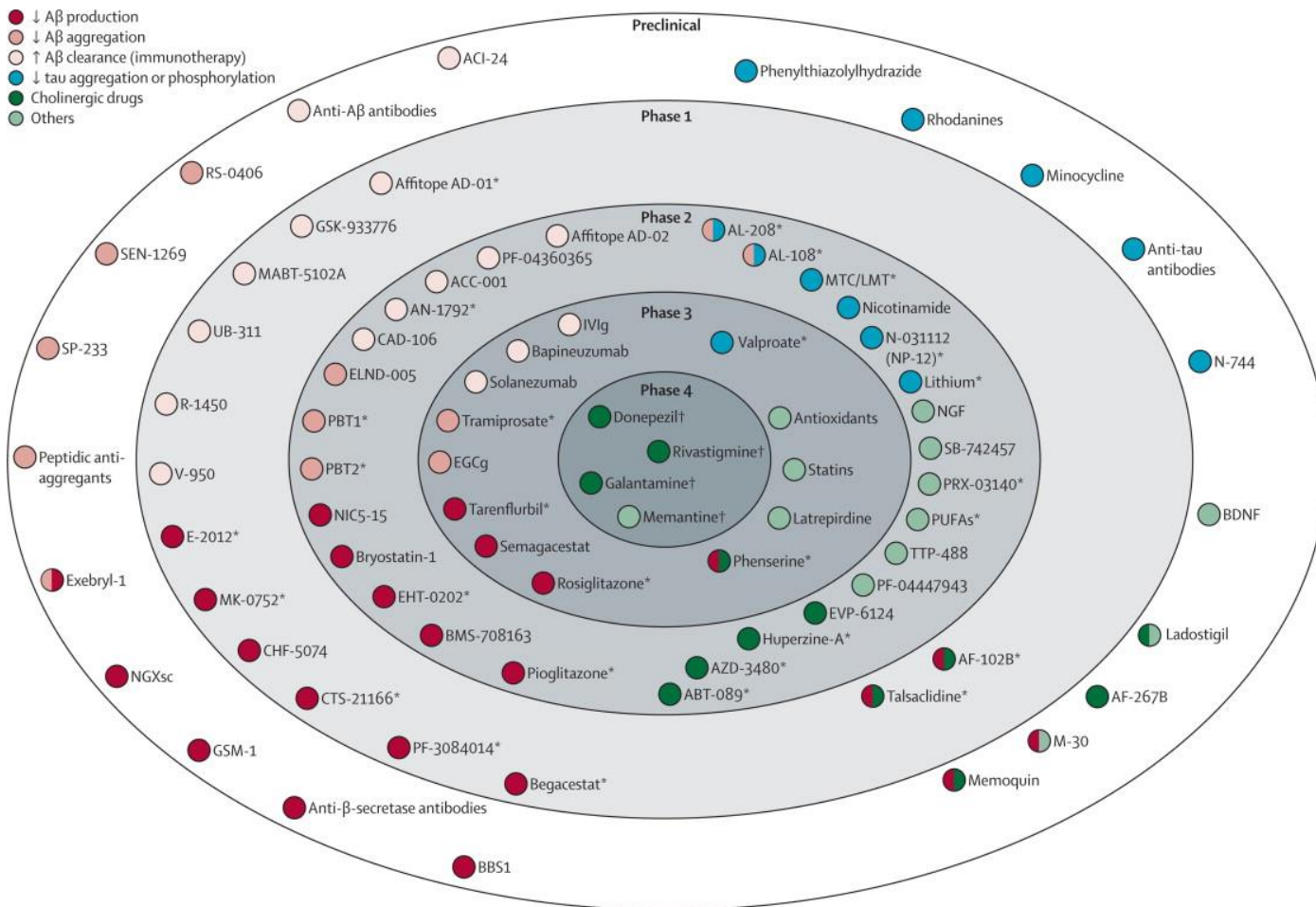
Charting the Course of Healthy Aging, MCI, and AD



Current state of treatments

- Anti-amyloid therapies have not been effective though some preliminary data for certain compounds
- Renewed focus on non-pharmacological/lifestyle interventions
- Focus on preventing dementia and enhancing cognitive reserve





WHO recommendations

- Physical activity
- Smoking cessation
- Alcohol control
- Proper nutrition
- **Cognitive training**
- **Social engagement**
- Cardiovascular management
- **Depression**



Can we prevent AD

- Focus on the concept of “successful aging”
- Defined by NIH working group as: “Not just the absence of cognitive impairment but the development and preservation of the multi-dimensional cognitive structure that allows the older adult to maintain social connectedness, and ongoing sense of purpose.”



Can we prevent AD

- Yaffe and Barnes, 2011, Lancet Neurology
- Recently reviewed modifiable risk factors for Alzheimer's disease and discovered that addressing 7 modifiable risk factors could reduce the incidence of AD by 25%
- Modifiable risk factors include diabetes, hypertension, obesity, depression, physical inactivity, smoking and cognitive inactivity



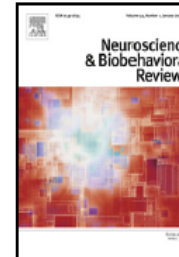


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Review

A review of physical and cognitive interventions in aging

P.D. Bamidis^{a,*}, A.B. Vivas^b, C. Styliadis^a, C. Frantzidis^a, M. Klados^a,
W. Schlee^c, A. Siountas^a, S.G. Papageorgiou^d

^a Group for Applied Neuroscience & Group for Assistive Technologies and Silverscience, Lab of Medical Physics, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, PO Box 376, 54124 Thessaloniki, Greece

^b Cognitive Psychology and Neuropsychology Lab, Department of Psychology, The University of Sheffield International Faculty, City College, 24 Proxenou Koromila, 54622 Thessaloniki, Greece

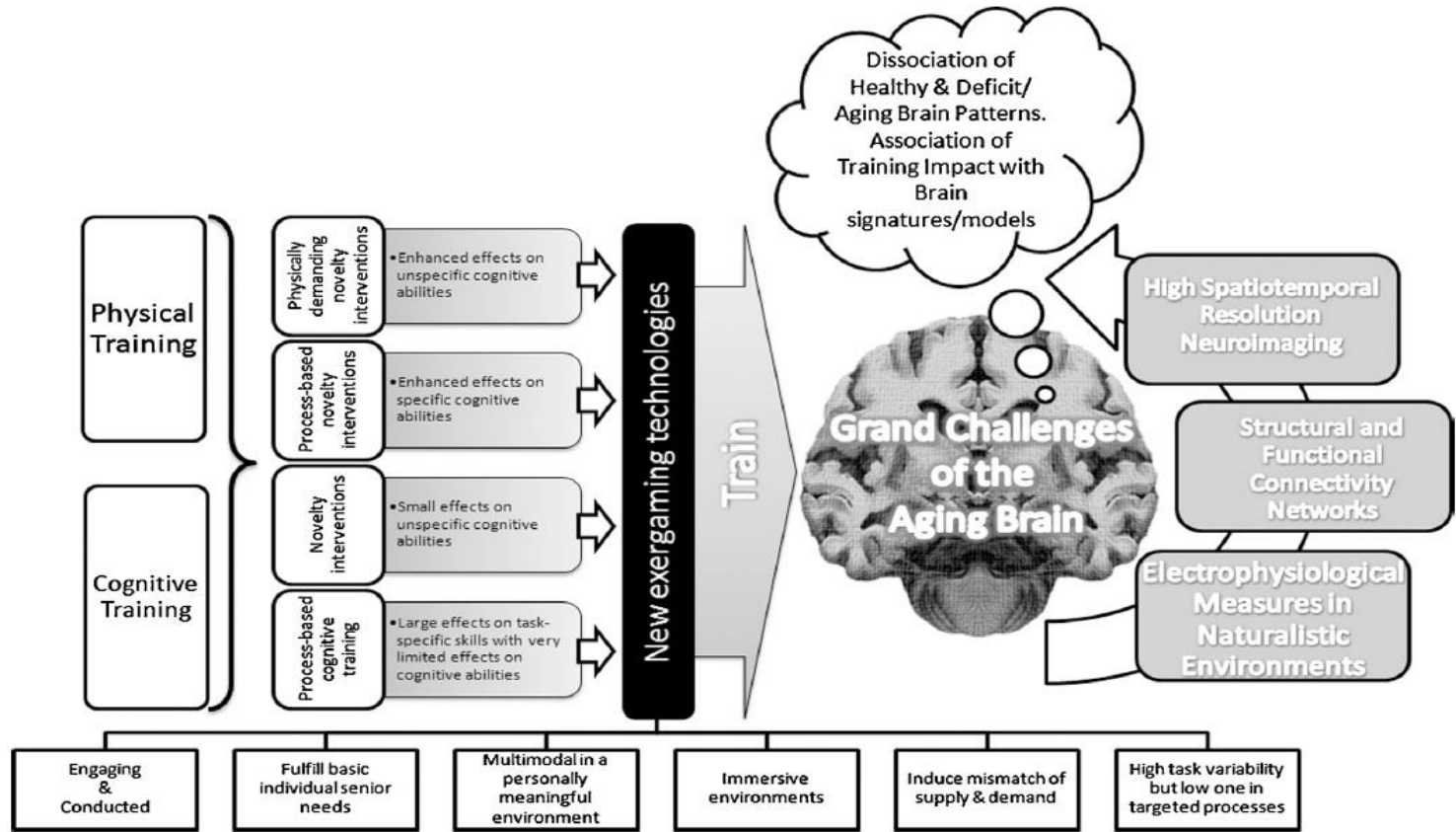
^c Department for Psychiatry and Psychotherapy, University of Regensburg, Universitätsstraße 84, 93053 Regensburg, Germany

^d Behavioral Neurology and Neuropsychology Unit, 2nd Department of Neurology, Medical School, University of Athens, University General Hospital ATTIKON, Athens, Greece



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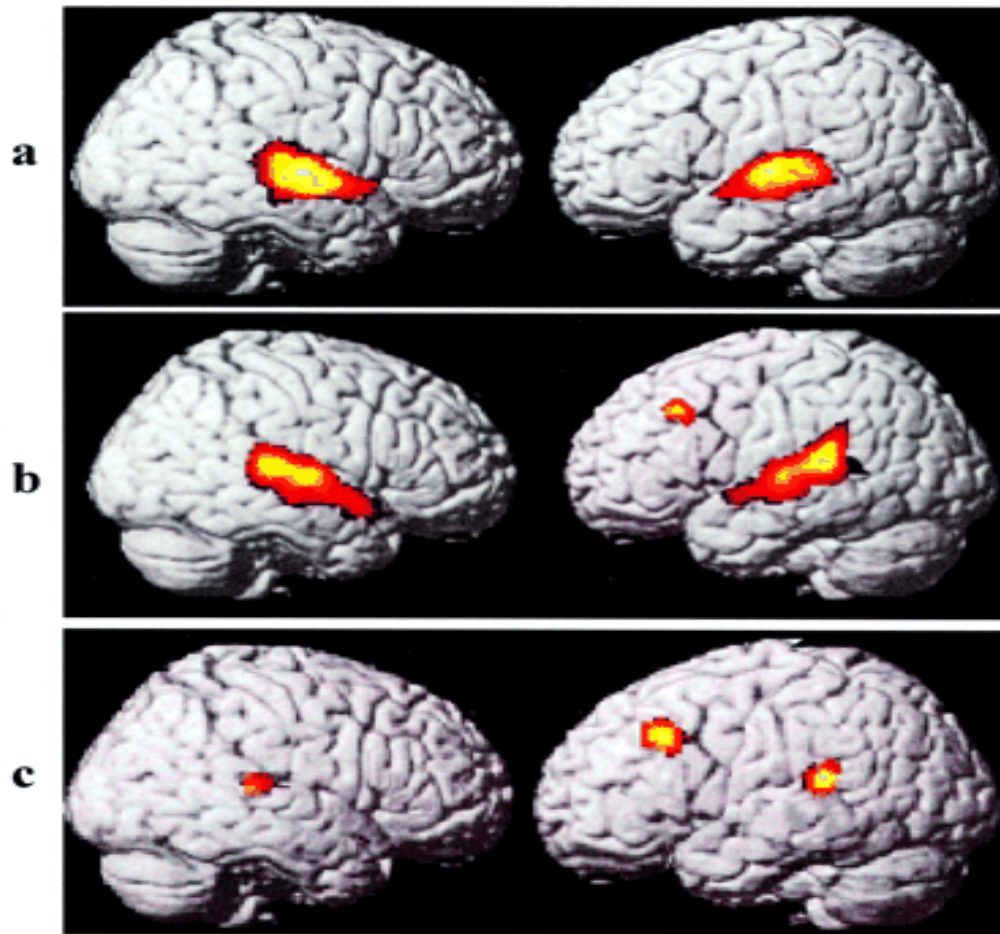
Why music



- Easily accessible
- Enjoyable, pleasurable
- Studies show it improves mood and anxiety symptoms (Thompson et al 2001)
- May increase neurogenesis, promote synaptic plasticity (Rickard et al 2005)



Brain surface projection of activated areas during passive music listening in control subjects and musicians.



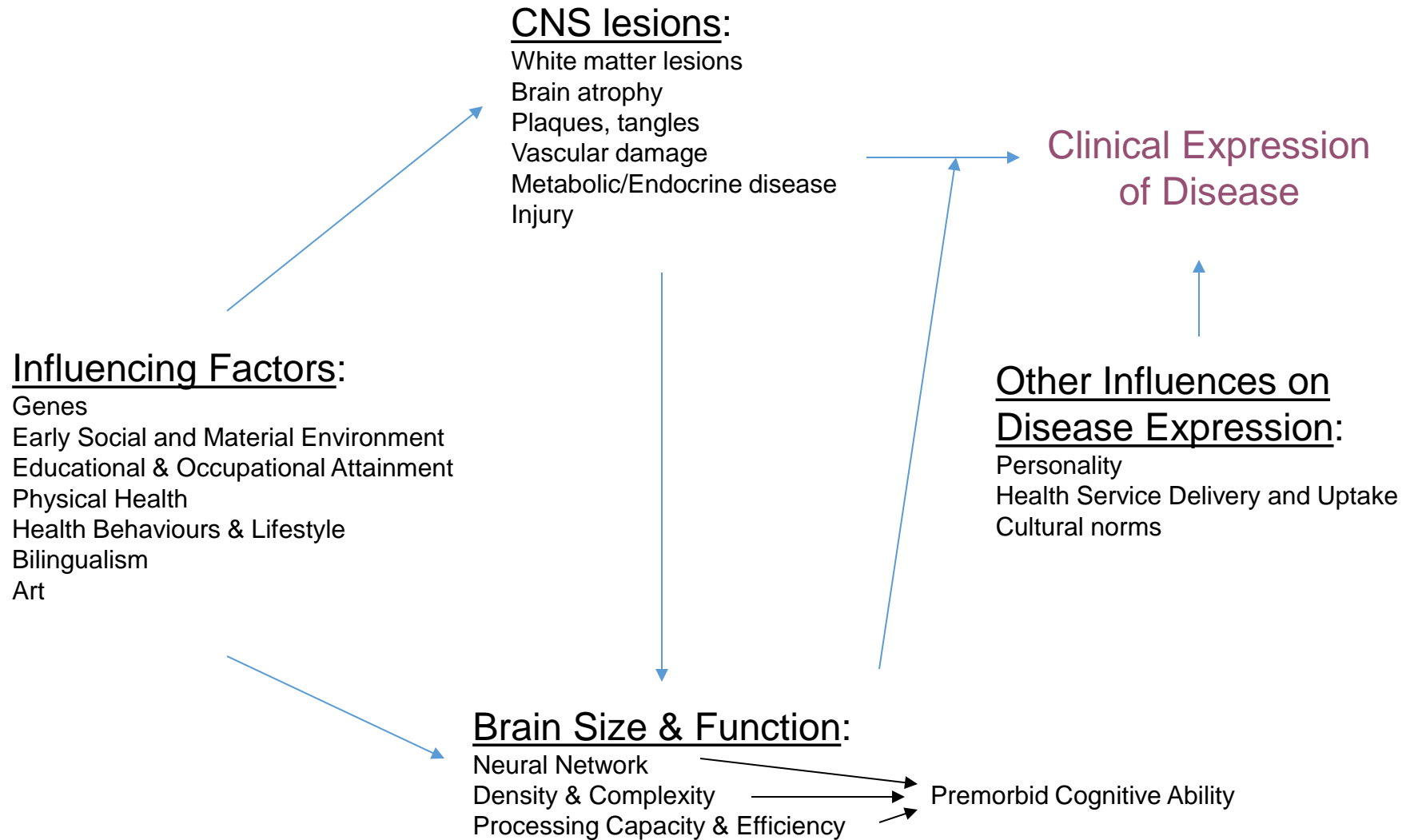
Source: Ohnishi T, Matsuda H, Asada T, *et al.* "Functional Anatomy of Musical Perception in Musicians. *Cerebral Cortex*, Aug 2001;11:754-760



Music Therapy as Behavioral Intervention in ADRD

Improve Sleep	Lindenmuth <i>et al.</i> , <i>J of Alz Dis & Rel Dis</i> 1992; 2:13-20.
Decreased Wandering	Fitzgerald-Cloutier. <i>Music Th Persp</i> 1992; 11:32-6.
Reduced Agitation	Brotons. <i>J of Music Th</i> 1996; 33:2-18.
Decreased Inappropriate Verbalizations	Casby. <i>Am J of OT</i> 1996. 48:883-339.
Diminished Aggressiveness During Bathing	Thomas. <i>J of Music Th</i> 1997. 34:246-59.





Alzheimer's disease and Music-based Interventions

- Music-based interventions (MBI) are inexpensive, enjoyable, provide positive participation (Lancioni et al), low drop out rates (Fang 2016)



Alzheimer's disease and Music-based Interventions

- Meta-analyses (Vasionyte and Madison 2013; Zhang et al 2017; Fang 2016) on MBIs utilizing individualized playlists for AD generally show
 - Positive effects of acute NPS, especially anxiety
 - Positive trend for cognitive (“most non-significant”)



Music intervention studies from 2013-2016

	Population	Method	Result
Arroyo-Anlli 2013 n=40	AD	At home listening to familiar music (vs unfamiliar music) for 12 weeks	✓ ↑ self consciousness
Sakamoto 2013 n=39	Severe AD	I = interactive (facilitator present) – clapping, singing, dance; P= passive (no interaction); 10 weeks	✓ ↓ stress, ↓ BPSD Interactive yielded better effects
Li 2015 n=52/30	AD	At home listening (Mozart) for 6 months	✓ abstraction, STM ✗ global cognition and daily functioning
Gallego 2016 n=42	Mild to moderate AD	6 weeks	✓ ↑ cognition (memory, orientation), ↓ depression, anxiety in all, ↓ BPSD in severe
Sanchez 2016 n=11/11	Severe to very severe AD	2x/week for 16 weeks	✓ ↓ agitation ✗ anxiety Multisensory stimulation yielded better effects

Inclusion criteria: AD only, n = 10+, English papers, music intervention










REVIEW ARTICLE

Front. Neurosci., 12 March 2019 | <https://doi.org/10.3389/fnins.2019.00132>



Music Intervention Approaches for Alzheimer's Disease: A Review of the Literature

 [Melissa Leggieri](#)^{1,2},  [Michael H. Thaut](#)³,  [Luis Fornazzari](#)^{1,4},  [Tom A. Schweizer](#)^{1,2,5},  [Joseph Barfett](#)^{1,6},  [David G. Munoz](#)^{1,2,7} and  [Corinne E. Fischer](#)^{1,2,8*}

¹Keenan Research Centre for Biomedical Research, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada

²Faculty of Medicine, Institute of Medical Science, University of Toronto, Toronto, ON, Canada

³Music and Health Research Collaboratory, Faculty of Music, University of Toronto, Toronto, ON, Canada

⁴Division of Neurology, Department of Medicine, University of Toronto, Toronto, ON, Canada

⁵Division of Neurosurgery, Department of Surgery, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

⁶Division of Nuclear Medicine, Department of Medical Imaging, St. Michael's Hospital, Toronto, ON, Canada

⁷Department of Laboratory Medicine and Pathology, University of Toronto, Toronto, ON, Canada

⁸Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, ON, Canada



Alzheimer's disease and Music-based Interventions

- Examined 6 studies that met criteria for our review
- Studies that used individualized playlists and focused on relaxation techniques yielded positive results
- Need for more rigorous studies combined with imaging



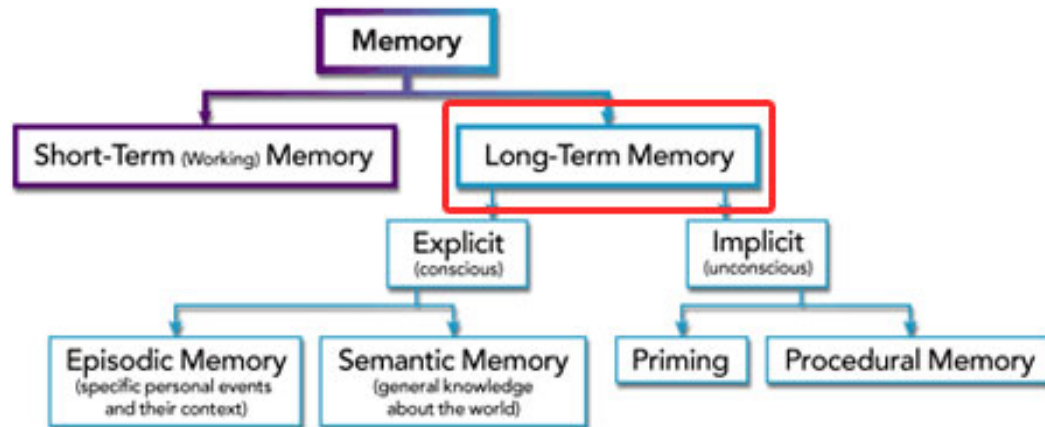
Aging and the Brain

- Normal aging involves grey matter volume decline
- Abnormal aging (AD spectrum) involves early decreases in temporal lobes
- Results in morphological brain changes and functional connectivity



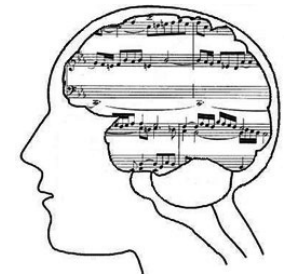
Musical Memory and AD

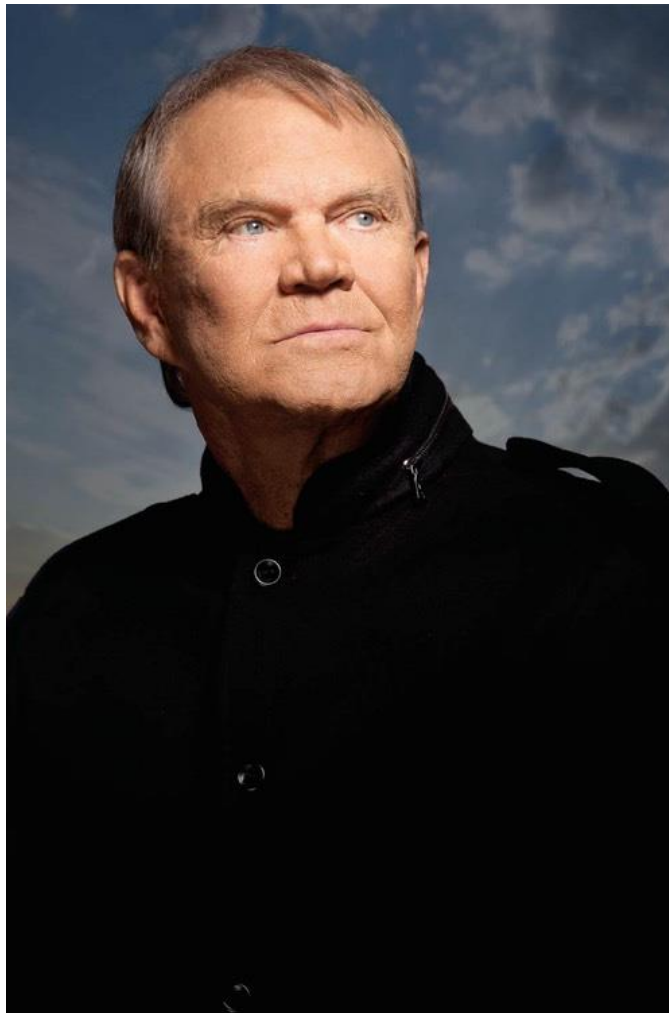
- Semantic musical memory: melody recognition, humming, whistling (Halpern and Zatorre, 1999; Platel et al., 2003; Schulkind, 2004; Groussard et al., 2009; Hailstone et al., 2009; Omar et al., 2010; Weinstein et al., 2011; Vanstone et al., 2012).
 - mainly in temporal and frontal areas



Musical Memory in AD

- Potential spared ability of music functions in AD has motivated the development of MBIs (review; Baird and Samson 2009)
- Explicit and implicit memory functions are comprised of separate neural networks
 - Implicit spared more often than explicit
- Musical memory networks are separate from other temporal lobe memory networks, and more broad





HIS COURAGEOUS FIGHT

As **Glen Campbell** battles Alzheimer's disease, family members share their stories of Glen's ongoing struggles.

STORY BY BOB PAXMAN

Two years ago, Glen Campbell came forward with a powerful, completely candid announcement that rippled throughout the entertainment world. With wife Kim by his side, Glen revealed that he had been diagnosed with Alzheimer's disease, the most common form of dementia, which eventually robs one of memory. It's an unpredictable illness of which there is no known cure, a frightening prospect for anyone, much less a renowned and influential entertainer of Glen's magnitude. But the family decided to make the announcement because they planned for Glen to embark on a series of farewell concerts, billed as the Glen Campbell Goodbye Tour, which kicked off later in 2011. Glen was also preparing to release a new album, *Ghost on the Canvas*, in August. They simply wanted the public to know that Glen was ill and might not be making music in the foreseeable future.



Glen Campbell

- Diagnosed with Alzheimer's disease in 2011 at the age of 75
- Started a farewell tour that include 151 shows
- In spite of advanced cognitive impairment, retained memory of music and able to perform



Preservation of episodic musical memory in a pianist with Alzheimer disease.

L Fornazzari et als.

Neurology 2006; 66: 610-611.-



Results (Table 1)

	MMSE	CDT	FAS	TMT	DRS	GDS	Global Det Scale	NPI
Baseline	Total-10 Atten-0 Mem-3	Command-7 Copy-4	19	A-200 B-220	AEMSS-0 Total-59	6/15	6	18
After Musical Testing	Total-6 Atten-0 Mem-1	Command-8 Copy-8	21	A-150 B-N/A	AEMSS-0 Total-63	1/15	6	12

MMSE: Mini Mental State Examination

CDT: Clock Drawing Test

FAS: Categories of F-A-S Test

TMT:
and Form B

DRS: Dementia Rating Scale (Mattis)

GDS: Geriatric Depression Scale

NPI: Neuropsychiatric Inventory
Trail Making Test – Form A



Original



Piano

5



Day 7 – 1 - Minute Recall



Results

- Over the course of the study, the subject was not able to recall any of the verbal material, whether it was presented in written or in auditory form. Likewise, she recalled nothing of the musical material presented to her in written form.
- However, she demonstrated a gradual learning and remembering of the auditory musical material, which she began to recall on day four.



Study 2

- Examined 2 patients from our clinic with moderate AD
- Both patients had a background in music and could play the piano
- Single blinded study in which patients were examined in their home x 7 days
- Recall of Anna Thompson story from the Weschler Memory Scale and bars from “Winter Scene”

[Can J Neurol Sci.](#) 2017 Mar;44(2):209-211. doi: 10.1017/cjn.2016.436.

Always in Tune: The Unforgettable Memory for Music in Alzheimer's Disease.



Study 2

- Neither patient regained memory of verbal material which was assessed one minute and 15 minutes exposure
- Both patients were able to gradually recall the musical material presented even though they had never been exposed to it before



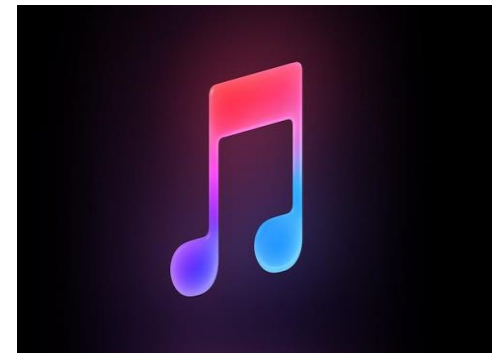
Music and autobiographical memory

- Autobiographical memory (ability to remember past personal events) deteriorated in AD
- Studies showed that **background music** improved autobiographical memory retrieval in **AD participants** (Foster and Valentine 1998; Foster and Valentine 2001; Irish et al 2006; El Haj 2015 al)



Music and autobiographical memory

- Self-chosen music has been found to evoke involuntary autobiographical memories relative to silence or investigator chosen music (El Haj 2012)
 - Specific
 - Emotional and impact mood
 - Quickly retrieved
 - Less executive control



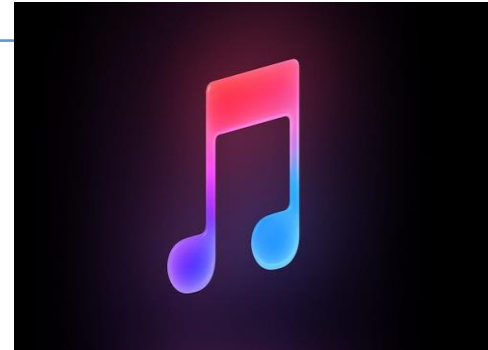
Music and autobiographical memory



- Experiment conducted by El Haj et al 2011
- 12 patients with mild AD were tested in three conditions: silence, exposed to opus 4 season and self chosen music
- Participants exposed to self-chosen music tested better on measures of autobiographical recall relative to other conditions



Music and autobiographical memory



- Experiment conducted by Foster and Valentine in 1998
- 20 patients with dementia were subject to autobiographical memory recall tasks
- Autobiographical recall was significantly better in the music condition relative to no music
- No effect of familiarity



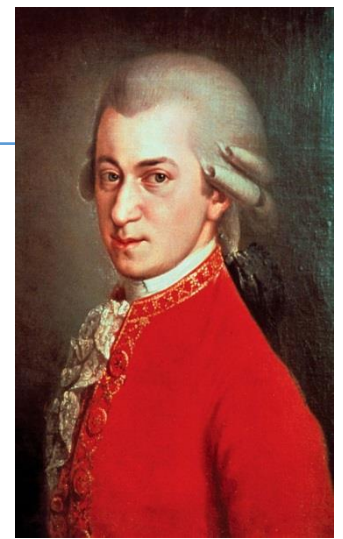


Music and autobiographical memory

- Study conducted by Irish et al in 2006
- Tested 10 patients with AD and 10 who were cognitively normal on autobiographical memory in silence and classical music (Vivaldi's spring from Four Seasons)
- Autobiographical memory recall improved for AD patients, correlated with reduced anxiety



Music and autobiographical memory



- Thompson et al 2001
- Participants were tested for spatial ability in silence, listening to a sad piece of music and listening to Mozart
- Participants that listened to Mozart had significant improvement in spatial scores relative to silence and sad music



Music and autobiographical memory

- Jacobson et al 2015 looked at brain activation associated with exposure to familiar music in young people
- 32 young health subjects were exposed to unknown, recently known and long known music
- Identified regions were then transposed on to brains of AD patients and healthy controls



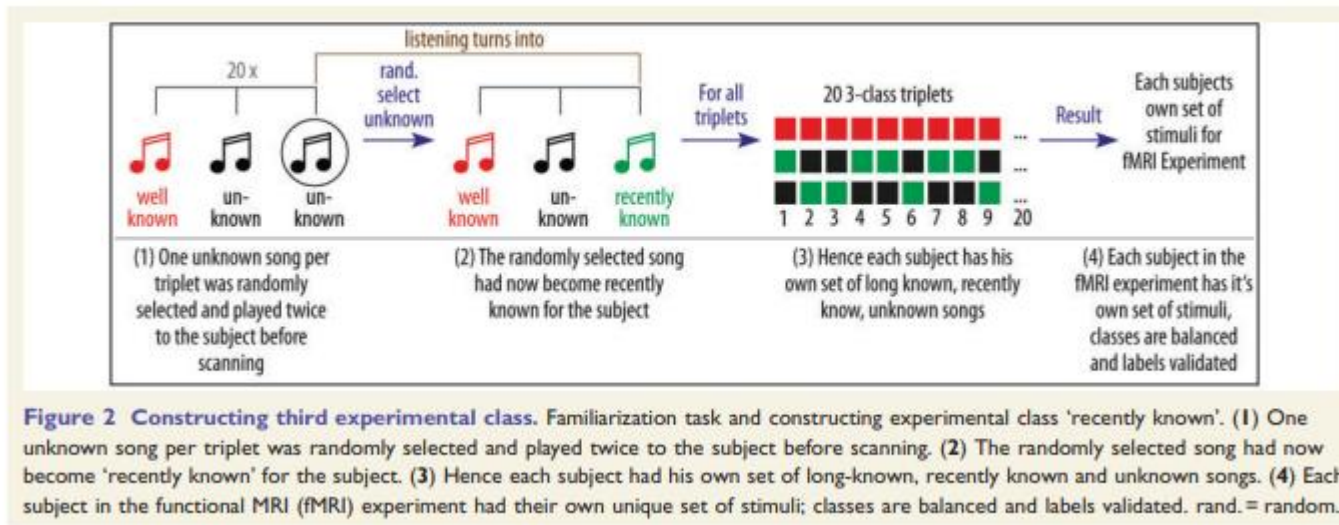


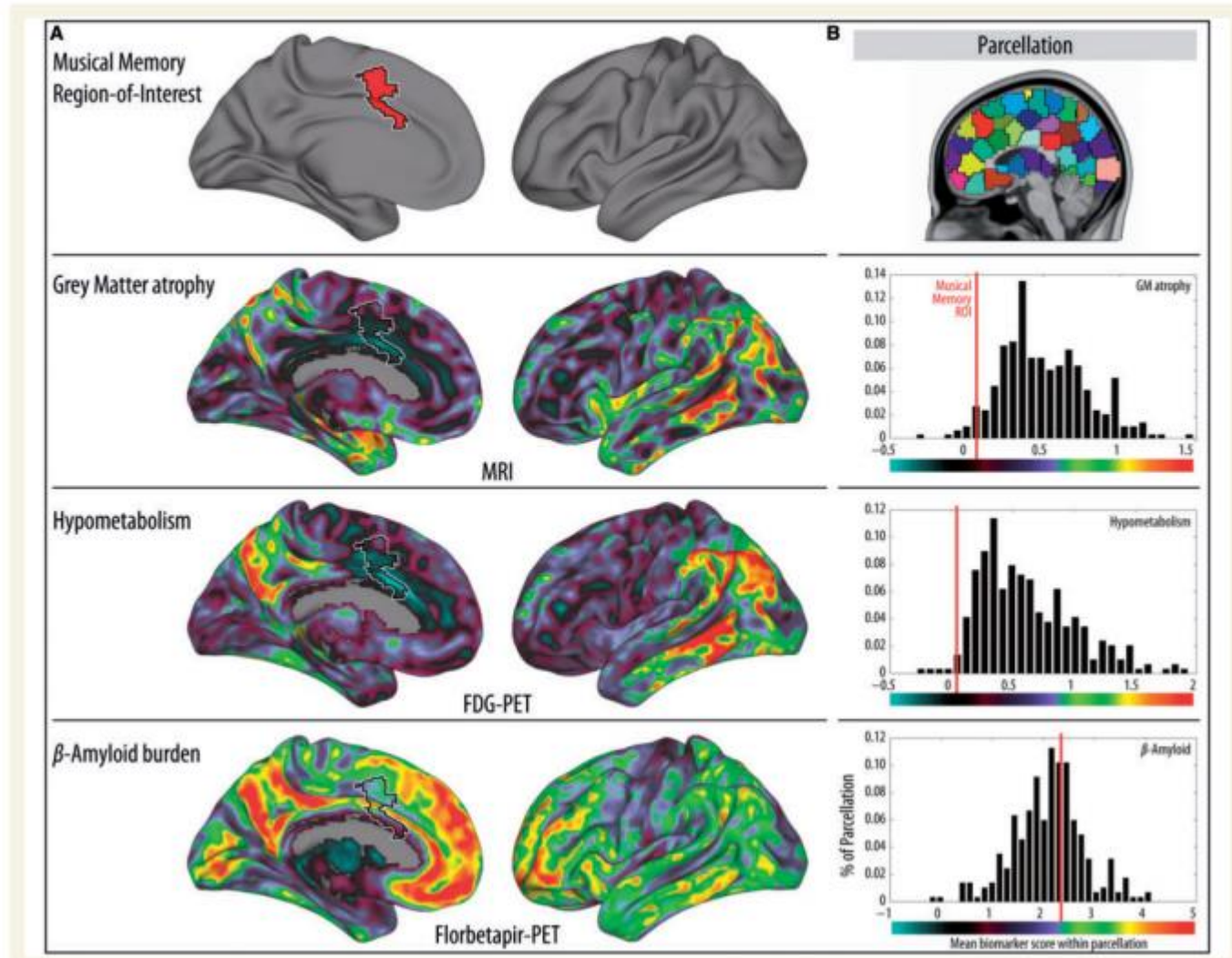
Figure 2 Constructing third experimental class. Familiarization task and constructing experimental class 'recently known'. (1) One unknown song per triplet was randomly selected and played twice to the subject before scanning. (2) The randomly selected song had now become 'recently known' for the subject. (3) Hence each subject had his own set of long-known, recently known and unknown songs. (4) Each subject in the functional MRI (fMRI) experiment had their own unique set of stimuli; classes are balanced and labels validated. rand. = random.



Music and autobiographical memory

- Identified brain regions included caudal anterior cingulate and ventral pre-supplementary area corresponded to long known musical memory
- When these brain regions were superimposed on AD brains there was no difference in amyloid deposition but less hypometabolism and atrophy suggest early changes





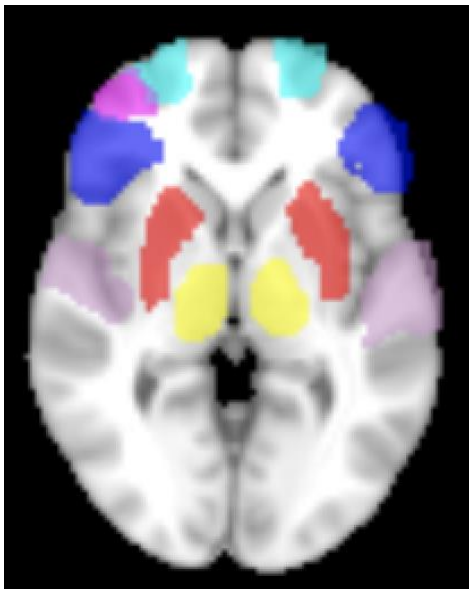
Music and autobiographical memory

- Study suggests that preservation of memory for familiar music may be mediated by involvement of brain structures that are affected by AD pathology only in later stages
- Provides a possible explanation for why music is preserved
- However subjects were young and findings were superimposed on to older subjects



Familiar music listening and aging (Sikka et al 2015)

50



37



Frontal areas

Inferior frontal

Orbital Middle Frontal

Superior frontal

Subcortical_areas

Putamen

Thalamus

Parietal areas

Supramarginal Gyrus

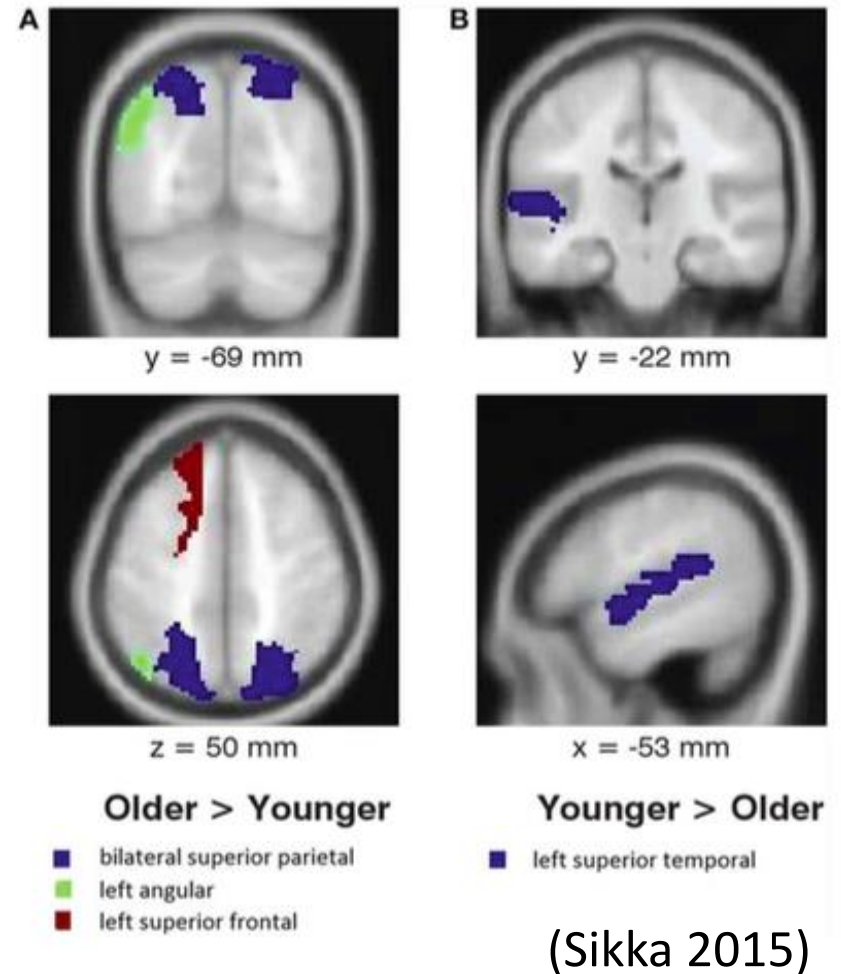
Temporal areas

Superior temporal gyrus



Familiar music listening and aging

- Older adults showed greater activation in the frontal lobe*, and parietal lobe
- Younger adults showed greater activation in the superior temporal



Studies examining familiar music exposure in AD

- 17 subjects with AD were exposed to a personalized music plan
- Post-intervention patients displayed greater SMA activation, corticocortical/cerebellar connectivity (King et al 2019)
- 34 AD patients compared to 19 controls
- Semantic memory localized to right inferior frontal cortex, episodic to posterior cingulate cortex (Slattery et al 2019)



Current Limitations in the Literature

- Musical memory networks have not been assessed in MCI/AD
 - Given extensive brain changes, unclear which brain areas are involved in musical memory and exposure
- No studies investigating the neuroimaging evidence of change in neural networks pre- and post-music intervention for AD/MCI
- All studies have only used “familiar” music



Goals

- To identify differences in brain activation patterns of long known music (LKM) recall versus unfamiliar music in patients with MCI/AD
- To determine whether repeated exposure to LKM (a **music intervention**) can modify brain activation in patients with MCI/AD
- To compare the effects of the music intervention at the level of network activation and cognitive performance



Hypotheses

Based on previous literature, we predict that:

- 1) AD/MCI participants exposed to long-known music over time will demonstrate improvement in memory scores
- 2) Improvement in memory scores will correspond to changes in activation of familiar music exposure (extensive frontal, parietal areas, as well as areas involved in emotion processing (subcortical, cerebellum))



Methods

Recruitment

- 10 MCI/AD musicians 9 MCI/AD non-musicians
- Participating recruitment sites
 - St. Michael's Hospital
 - Memory Clinic at St. Michael's Hospital (Dr. Fischer and Dr. Fornazzari)
 - Long term care homes
 - Belmont House
 - Wellesley and Re kai Centres
 - Performing Arts Lodge (PAL)



Protocol

Prior to Participation

- Participants were screened for inclusion and had to meet criteria for AD/MCI according to NIA criteria
- Had to have adequate hearing, able to undergo and MRI
- RA called participants and obtained list of long-known, autobiographically salient music defined as music known by the participant for at least 20 years



Protocol

Part 1

- **Pre-scan interview:** Participant will listen to the “Long-known music playlist” and “Unknown music playlist”
- **Behavioural Testing:** Participants complete the demographics questionnaire and MoCA (Cognitive) and caregivers were given the NPI-Q (Behavioural)
- **MRI Paradigm:** Listening to long-known music and recently heard music we mapped brain activation



Protocol

Part 2

Music listening intervention

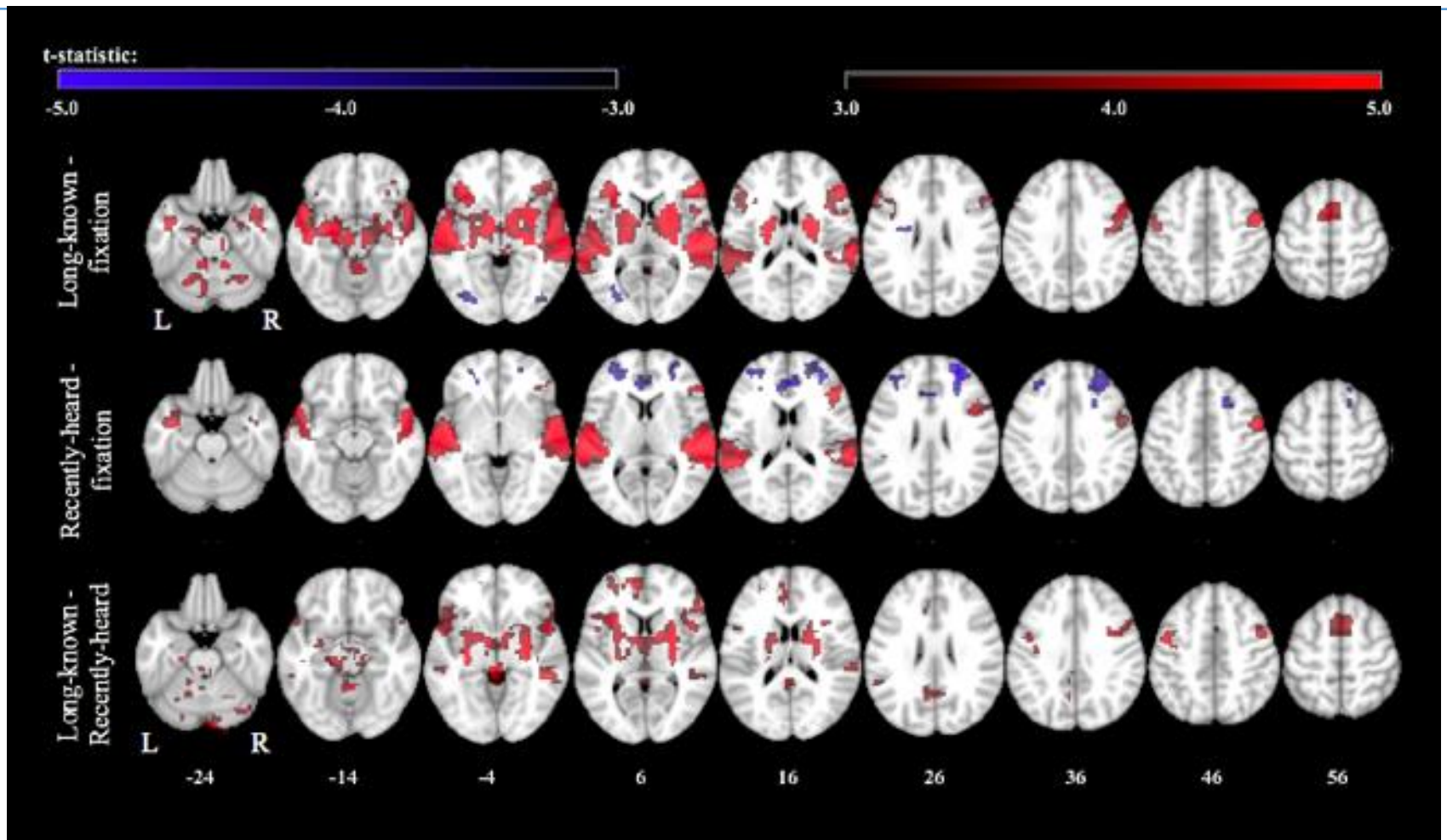
- Participants is given an MP3 player with long-known music to listen to 60 minutes a day everyday for 3 weeks
 - Structured, remembering past experiences during listening (not passive listening)
- Study informant will be called and asked if participant is appropriately participating in music listening intervention



Table 1. Demographic characteristics, baseline cognitive presentation of persons with MCI, early AD, and all participants.

	MCI (n=13)	early AD (n=4)	All participants (n=17)
Age, years	70.9 ± 10.1 (56-88)	79.2 ± 8.8 (70-89)	72.9 ± 10.2 (56-89)
Sex, n (%)	11 female (85%) 2 male (15%)	3 female (75%) 1 male (25%)	14 female (82%) 3 male (18%)
Education, years	15.7 ± 2.2 (12-18)	14.5 ± 3.7 (12-20)	15.4 ± 2.5 (12-20)
Bilingual, n (%)	5 (38%)	1 (25%)	6 (35%)
Depression, n (%)	0 uncontrolled (0%) 3 controlled (23%) 10 none (77%)	0 uncontrolled (0%) 0 controlled (0%) 4 none (100%)	0 uncontrolled (0%) 3 controlled (18%) 14 none (82%)
MMSE total score	27.3 ± 1.3 (25-29)	26 ± 2.2 (23-28)	27.0 ± 1.6 (23-29)
MoCA total score	23.1 ± 2.0 (19-25)	22.2 ± 2.6 (20-26)	23.1 ± 2.1 (19-26)





Baseline Study Results

- Study showed LKM was associated with more widespread brain activation relative to unknown music
- Also found greater frontal lobe activation in SMA and precentral gyri, as well as the IFG
- Subcortical regions, such as the anterior insula, putamen, pallidum and anterior thalamus
- Precuneus activated bilaterally
- Consistent with prior studies (King et al 2019, Slattery et al 2019)



Post-Intervention Study Results

- Exposure to unknown music showed no change
- Exposure to LKM showed **de-activation** in the following brain regions: the right precentral gyrus, as well as the bilateral SMA, IFG, putamen and pallidum
- These were the same brain regions that showed activation with familiar music exposure



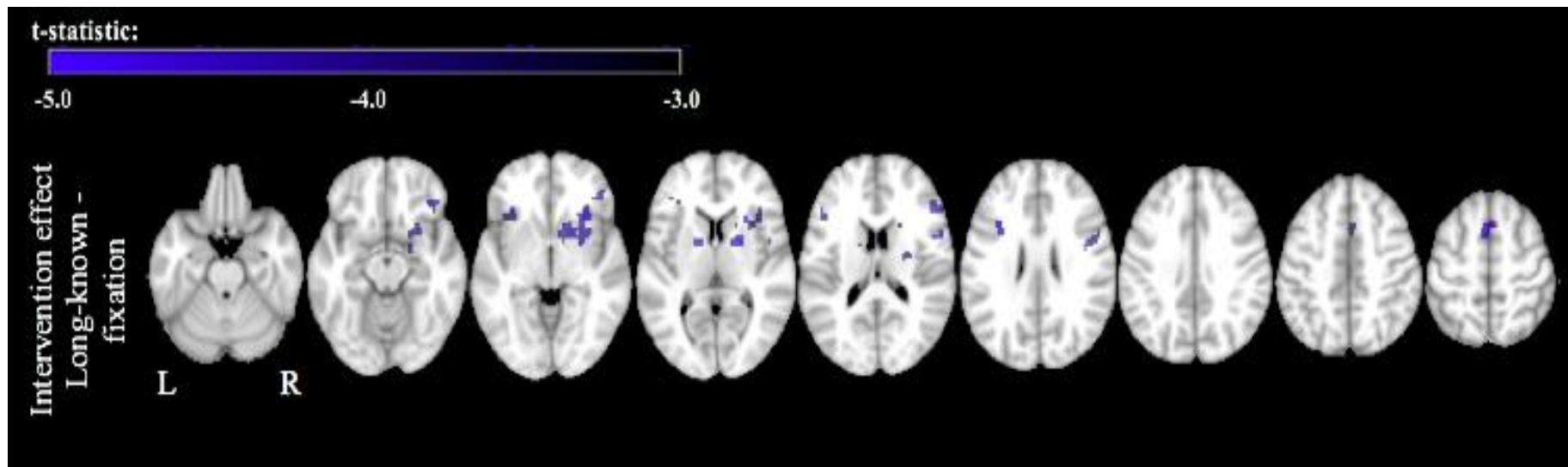


Table 3. Comparison of Pre- and Post-MBI MoCA scores in all participants

	Baseline MoCA score (n=14)	Post MBI MoCA score (n=14)	p-value
Visuospatial/ Executive function (/5)	3.3 ± 0.91 (2-5)	3.7 ± 0.61 (2-4)	0.130
Naming (/3)	2.6 ± 0.50 (2-3)	2.8 ± 0.43 (2-3)	0.317
Attention (/6)	5.6 ± 0.50 (5-6)	5.8 ± 0.43 (5-6)	0.414
Language (/2)	2.2 ± 0.70 (1-3)	1.9 ± 0.95 (0-3)	0.132
Abstraction (/2)	1.6 ± 0.65 (0-2)	1.6 ± 0.50 (1-2)	0.739
Memory (/5)	2.0 ± 1.9 (0-5)	2.4 ± 1.20 (0-5)	0.034*
Orientation (/6)	5.9 ± 0.36 (5-6)	5.9 ± 0.36 (5-6)	1.000
Total Score (/30)	23.4 ± 2.06 (20-25)	24.2 ± 2.64 (20-27)	0.100



Discussion

- This is the first study to examine changes in brain activation associated with a structured long-known music listening regimen
- Areas of activation are similar to Sikka et al (2015), the only study to include older adults in a familiar music listening task



Discussion

- Significant activation of areas involved in emotion may be due to explicit recall of autobiographical memories associated with music, relative sparing may be due to minimal amyloid deposition
- Provides a possible explanation for why musical memory is more resistant to neurodegeneration



Discussion

- Older adults with cognitive impairment see more extensive, bilateral activation when recalling musical memories, significant subcortical activation
- Decreases in frontal/memory areas in recently heard music show almost no cognitive stimulation during listening



Discussion

- Repeated exposure to music which evokes memories can change brain activity after only 3 weeks, specifically in those with a musical background
 - Cognitive scores approaching significance
 - Can music have therapeutic benefits beyond just effects on mood
 - Is familiar music cognitive enhancing



Summary and future directions

- There is substantial evidence that music is beneficial for the brain
- Memory for music may be more resistive to neurodegeneration
- Autobiographically salient music exposure may lead to more widespread brain activation
- This may in turn improve cognitive functioning





L'Enciclopedia 1751

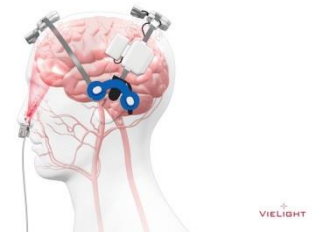
“If one reflects somewhat upon the connection that discoveries have with one another, it is readily apparent that the sciences and the arts are mutually supporting and that consequently there is a chain that bonds them together”

J D'Alembert, D Diderot, JJ Rousseau, Voltaire, Montesquieu, B d'Helbach, B de Condillac



Clinical Trials in Alzheimer's Disease at St. Michael's Hospital

- Ganterumab for patients with prodromal AD/AD (anti-amyloid compound)
- Azeliragon (TTP 448) for patients with prodromal AD/AD and impaired glucose tolerance (RAGE inhibitor)
- Vielight neuro gamma RX for AD patients with moderate to severe AD



If interested in clinical trials please contact:

Komal Talib at 416-864-6060ext7838

Komal.Talib@unityhealth.to

Dr. Corinne Fischer 416-864-5320

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- Dr. Michael Thaut
- Dr. Tom Schweizer



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Thank you!

