Round table: Moderator; Fereshteh Sedaghat, MD, PhD

Brain Mapping in Dementias and Non-invasive Neurostimulation

1. Reflection of Mild Cognitive Impairment (MCI) and Dementias by Molecular Imaging, PET and SPECT
Fereshteh Sedaghat, MD, PhD, Private Outpatient Cognitive Neuroscience Clinic, Mashhad-Iran, Nuclear Medicine specialist, Neuroscientist

2. Contribution of Genetic Neuroimaging Factors on the Conversion of Mild Cognitive Impairment (MCI) to Alzheimer's Disease (AD): Linking Structural and Functional Brain Changes to the Pathophysiology of AD
Stavros Dimitriadis, PhD
Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, UK, Artificial Intelligence and Information Analysis Laboratory, Department of Informatics, Aristotle University, Thessaloniki
Brain Mapping in Dementias and Non-invasive Neurostimulation

3. Transcranial electrical current stimulation (tDCS, tACS, tRNS) - basics, functional mechanisms and potential application in mild cognitive impairment (MCI) and neurodegenerative diseases

Prof. Michael A. Nitsche, MD

Scientific Director of the Department of Psychology and Neurosciences at the Leibniz Research Centre for Working Environment and Human Factors in Dortmund, Germany

Staff member at the Dept. Neurology of the University Medical Hospital Bergmannsheil, Bochum, adjunct member of the psychological faculty of the University of Bochum, and Member of the International Graduate School for Neurosciences at Bochum University.

4. A brief Introduction to Audio-Visual Stimulation and Neurofeedback

Fereshteh Sedaghat, MD, PhD, Private Outpatient Cognitive Neuroscience Clinic, Mashhad-Iran
• Any Questions at the end of the session please
• Thank you
Reflection of Mild Cognitive Impairment (MCI) and Dementias by Molecular Imaging, PET and SPECT

Fereshteh Sedaghat M.D. Ph.D.

Sedaghat Outpatient Cognitive Neuroscience Clinic, Mashhad, Iran, fereshsedag@yahoo.com
Dementia

- Impairment in at least 2 cognitive domains, beyond what might be expected from normal aging, severe enough to interfere with daily functioning.
Most common types of dementia

- Alzheimer; 55%
- Lewy body; 20%
- Vascular-Stroke-Mixed; 15%
- Traumatic brain Injury; 4%
- Frontotemporal dementia; 6%
- Other; 4%
Age-standardised dementia mortality (Alzheimer's disease) 1971 to 2013
Dementia is on the Increase compared to other major leading causes of Death

Changes in number of death
A comparison of years 2000-2008 and 2000-2010

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>HIV</th>
<th>Stroke</th>
<th>Heart disease</th>
<th>Prostat cancer</th>
<th>Brest cancer</th>
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<tbody>
<tr>
<td>2000-2008</td>
<td>66%</td>
<td>-29%</td>
<td>-20%</td>
<td>-13%</td>
<td>-8%</td>
<td>-3%</td>
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<tr>
<td>2000-2010</td>
<td>68%</td>
<td>-42%</td>
<td>-18%</td>
<td>-16%</td>
<td>-8%</td>
<td>-2%</td>
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Statistics derived from Alzheimer's Association
Diagnosis

• The diagnosis of dementia in the early stage is problematic and the definite diagnosis needs autopsy or biopsy (rarely done)
• Structural brain imaging (CT, MRI) is useful to study morphological changes of the brain

• Single photon emission tomography (SPECT) and positron emission tomography (PET) help us to study physiology and functional changes of the brain (blood flow, metabolism)
Brain Perfusion Study

Lipophilic, Cross intact BBB, undergo hydrophilic conversion
Study of the metabolism

- PET uses fluorine 18 ($^{18}$F)-labeled fluorodeoxyglucose (FDG), an analogue of glucose.

- FDG is taken up by high-glucose using cells such as brain, kidney, and cancer cells. FDG cannot be further metabolized in cells.
CBF and metabolism are coupled to neuronal activity in most conditions.
CT and MRI, have long played a supportive role in the diagnosis of cognitive impairment and are recommended for the evaluation of AD.

Coronal T2-weighted fast spin-echo MR images a patient with AD and an age-matched control. The patient with AD has severe bilateral hippocampal atrophy (arrows).
SPECT of the patients with AD typically demonstrates reduction of perfusion in the temporoparietal regions.

67-year-old female. Global decrease in blood flow to all cortical structures, with accentuation of the decrease in the posterior temporal parietal region. Relative sparing of the basal ganglia, sensorimotor cortex, cerebellum in AD.
3 dimensional surface rendered images in SPECT

N

AD
PET also demonstrates deficits in temporoparietal metabolism in AD.
Sensitivity and specificity of SPECT and PET

The overall accuracy of FDG PET in detection of AD is superior to SPECT,

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<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td>PET</td>
<td>87%-90%</td>
<td>85%-92%</td>
</tr>
<tr>
<td>SPECT</td>
<td>58%-100%</td>
<td>60%-100%</td>
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*Ronald L Van Heertum et al, Semin.Nucl.med, 2003*
Early diagnosis is an important goal

• Several SPECT and PET studies show reduced perfusion and glucose metabolism in entorhinal cortex, precuneus and posterior cingulate region of the individuals with mild cognitive impairment (MCI) and in those with genetic factors of apolipoprotein E4 (APOE 4) allele, years before the symptoms of dementia be appeared.

Nobili et al. Journal of Alzheimer’s Disease 17 (2009) 761–772
FDG-PET medial temporal lobe uptake

- male, age 66 years, 16 years education, MMSE = 30
- female, age 67 years, 14 years education, MMSE = 30
- male, age 66 years, 14 years education, MMSE = 23

normal (dashed arrow) or questionable cortical uptake
reduced (solid line) MTL uptake in MCI.
Scans of a patient with mild cognitive impairment (MCI) (female, age 75 ), showing normal hippocampal and entorhinal cortex volumes on MRI and reduced FDG uptake on PET.
Neurotransmitter and receptor imaging

• Reductions in the acetyl cholinesterase enzyme in AD brains has been demonstrated in vivo with PET using different tracers for acetyl cholinesterase as N-\([^{11}C]\) methylpiperidine-4-yl propionate.
PET imaging of nicotinic acetylcholine receptors in AD, MCI

PET and SPECT can also be used for dopaminergic system imaging

Simplified diagram of a striatal dopaminergic synapse.

Booij & Kemp. EJNMMI(2008)
- Dopamine transporter (DaT) is a protein situated on the presynaptic membrane of dopaminergic neurons, which takes part in the reuptake of dopamine and in this way play a role in synaptic content of dopamine.
• Ioflupane a ligand derived from cocaine, also called FP-CIT labeled with radioactive 123I is used in order to quantify presynaptic dopamine transporter in the striatum by means of SPECT and is a good biomarker in differential diagnosing of parkinsonism.
Dementia with Lewy bodies is an under-recognized cause of dementia. Occipital (BA18-19) hypoperfusion and hypometabolism, differentiating it from AD.

Gilman S et al, 2005
Presynaptic dopamine transporters imaging (DaT scan) in DLB

Several SPECT studies show a reduction of the presynaptic dopamine transporters in striatum, distinguishing DLB and AD.

Sedaghat F et al, J Neurodegenerative dis. 2007
Degeneration is limited to the frontal and temporal lobes.

Early Pick’s disease

67-year-old female with a rapidly progressing frontal lobe type dementia. The MRI scan shows mild atrophy in the sylvian regions but no frontal lobe atrophy.

Marked reduction of tracer uptake in the frontal lobes which is not due to cortical gray matter loss but reduction of neuronal activity.
Amyloid B and P Tau
Neuropathologic hallmarks of AD
Imaging Neurofibrillary tangles (tau PET)

To label a scan abnormal, we propose that a scan with tracer uptake confined to the medial temporal lobes would not be considered positive but a scan with uptake in AD-like isocortical areas would. Gives us relatively late appearance of tau pathology so it may not be useful for early diagnosis.
Imaging Amyloid deposits

• There are several ligands such as $[^{11}C]PIB$ and florbetapir that bind to Aβ deposits in the brain and let us to study Aβ accumulations in living humans.


Chemical structures of amyloid PET tracers
MRI, FDG-PET and PIB-PET of a normal control and an AD patient

Mistur et al 2009
Florbetapir that binds to fibrillar amyloid in vivo and shows great potential for early detection. Right column depicts Aβ antibody reactivity by immunohistochemistry in postmortem specimens from the same subjects. Note correlation between radiotracer uptake and antibody reactivity.

Clark et al JAMA 2011
• A significant proportion, 15% (ranging from 2 to 32%) of patients have a negative amyloid-β scan
• Some cases of Aβneg-AD might correspond to false negatives due to technical issues or scan misinterpretation, or a lack of sensitivity of amyloid-β ligands in cases with low amyloid-β burden

(Cairns et al., 2009; Rosen et al., 2010; Scho¨ ll et al., 2012; Johnson et al., 2013)

• The majority of Aβneg-AD cases probably reflect clinical misdiagnosis, as the accuracy of the clinical diagnosis of probable Alzheimer’s disease at expert centers is 70% when compared to the cause of dementia as determined at autopsy

• Patients with a negative amyloid positron emission tomography scan following an initial clinical diagnosis of Alzheimer’s disease have heterogeneous clinical presentations and neuroimaging profiles;
Heterogeneity of Alzheimer's disease result in difficulties in its diagnosis and therapy

**Heterogeneity:**

- **Neuropathological**
  - Different pathologies that distributed similarly present similarly (false positive error)

- **Pathophysiological**
  - Similar pathologies that distributed differently present differently (false negative error)

- **Clinical**
  - Multiple pathologies coexist in an individual (false negative error)
First Guidelines published for brain amyloid imaging

- Those who complain of persistent or progressive unexplained memory problems using standard tests of cognition and memory

- Individuals meeting criteria for possible Alzheimer's but who are unusual in their clinical presentation

- Individuals with progressive dementia and atypically early age of onset (before 65)

Alzheimer's Association 2013
Amyloid-PET doesn’t reflect the severity of cognitive decline. More abnormal values in other of these biomarkers are strongly associated with worse cognitive symptoms throughout the clinical spectrum.
CONCLUSION

Diagnostic and therapeutic strategies arose from our increasing understanding of:

• AD pathology
• Distribution patterns of pathology

which can be reflected by PET and SPECT.
Meanwhile focusing on non-pharmacological approaches for improving the quality of life, elimination of potential risk factors of the disease and cognitive enhancement are recommended.

Thank you