Identifying Alzheimer's disease earlier and easier: new method on the horizon?

Dr. Florian Metzger, Geriatric Center and Department of Psychiatry und Psychotherapy University of Tuebingen
Why is an early diagnosis essential?

Medical Intervention: The earlier, the more efficient

- Medicative treatment
- socio-therapeutic
  - physical exercise
  - cognitive activity
  - stimulating
  - social environment
- Optimally: combination
  (Heuser 2006)

Intervention in the advanced stage of the disease only symptomatic for accessory symptoms.
Identifying Alzheimer's disease earlier and easier: new method on the horizon?

Alois Alzheimer

Described Alzheimer's Disease for the first time at 3./4.11.1906

"Über eine eigenartige Erkrankung der Hirnrinde" post mortem – very late stage Auguste D. (Nov. 1902)
Biomarkers in the Continuum of Alzheimer

When and where are the points of Diagnosis?

Parvizi et al., 2001; Rüb et al., 2001; Braak et al., 2004, 2006
Identifying Alzheimer's disease earlier and easier: new method on the horizon?

Where are the first changes?
M. Alzheimer: Clinical stages and involved brain regions according to Braak (2004)
Where are the first changes?

Clinical evidence for the involvement of the brainstem in the context of M. Alzheimer

- increased cardiovascular mortality for AD (Beard 1996)

- dysfunction of the autonomous brainstem nuclei (Thompson et al., 2007)
Identifying Alzheimer’s disease earlier and easier:
new method on the horizon?

AD in the brain stem

Evidence for the involvement of the brainstem in the context of M. Alzheimer

Parvizi 2001: demonstration of neurofibrillary tangles (NFTs) and senile plaques (SPs)

b: yellow – NFTs
dark green – SPs
light green – both
c: purple – severely affected
gray - moderate

Parvizi J, Van Hoesen GW, Damasio A: The Selective Vulnerability of Brainstem Nuclei to Alzheimer’s Disease
Identifying Alzheimer's disease earlier and easier: new method on the horizon?

N. Vagus = X. cranial nerve

Miscellaneous Cranial nerve
- sensory: ear, pharynx, larynx
- motoric: larynx, pharynx
- autonomous nervous system: gastro-intestinal tract, heart
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N. Vagus = X. cranial nerve

Broad projections in nearly all brain areas:
- basal forebrain
- brainstem
- raphe nuclei (serotonergic)
- Locus coeruleus (noradrenergic)
- numerous cortical areas

(Vonck 1995)
Stimulation of the N. Vagus

Therapeutic stimulation

Indications:

• Epilepsy
• Depression
• Anxiety
• Neuroenhancement in AD
• Migraine

Duncan A. Groves, Verity J. Brown: Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects Neuroscience and Biobehavioral Reviews 29 (2005) 493–500
Stimulation of N. Vagus

Therapeutic Stimulation of the N. vagus (VNS):
at the thoracic main stem
R. Auricularis N. Vagi = Cutaneous branch of the X. cranial nerve

Cutaneous representation of the N. vagus in the external auditory canal including the inner side of the tragus via the R. auricularis N. vagi (Peukert und Filler 2002)
R. Auricularis N. Vagi = Cutaneous branch of the X. cranial nerve

First theoretic consideration by E. C. Ventureyra in 2000:
Stimulation of the R. auricularis N. vagi
as strategy of antiepileptic therapy

Ventureyra ECG, Transcutaneous vagus nerve stimulation for partial onset seizure therapy, Child’s Nerv System 16: 101–102

Diagnostic application for the first time by A. J. Fallgatter 2003:
Evoked potentials of the N. Vagus:
Far field potentials from the brain stem after transcutaneous vagus nerve stimulation.

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Evoked Potentials

- Neurologic clinical method
- aims: conductance and function of neural pathways
- established in neurology for 50 years
- functional impairment is measured before structural lesions

- Clinically often used evoked potentials:
  - visual
  - somatosensory
  - motoric
  - acoustically
  - Blinking reflex
Evoked Potentials

Example:

Acoustically Evoked Potentials (AEP)

Stimulation of a sensory organ (AEP: ear) or of a peripheral nerve → electrical potential in active brain region
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Acoustically Evoked potentials

In case of structural or functional lesions: Change in the typical course of the potential

acoustic neuroma
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Vagus Somatosensory Evoked Potentials - Basics
Identifying Alzheimer's disease earlier and easier: new method on the horizon?

Vagus somatosensory evoked potentials

C3 - F3
C4 - F4
Fz - F3
Fz - F4

N1
P1
P2
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Vagus somatosensory evoked potentials

P1 – characteristic latency: 1 – 4 ms
N1 – characteristic latency: 2 – 6 ms
P2 – characteristic latency: 4 – 8 ms
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Vagus somatosensory evoked potentials

Stimulation via:

- very fine copper stranded wires
- fixed with paste at the inner side of the tragus
- cathode and anode are approx. 5 mm apart from each other
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Vagus somatosensory evoked potentials

Stimulation parameters:
- electrical square impulses
- duration 0.1 ms
- intensity 8 mA
- frequency 0.5 Hz
Vagus somatosensory evoked potentials

Recording: EEG-electrodes
International 10-20-system
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Vagus somatosensory evoked potentials

Recording parameters:

- sampling rate 20 KHz
- bandpass of 0.1 Hz to 1 KHz
- epoch length 10 ms
- Averaging of 100 artifact free epochs
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Vagus
Somatosensory
Evoked
Potentials – Methodological Aspects
Vagus somatosensory evoked potentials

VSEP are only measureable in Vagus supplied areas:

- Inner Tragus and Meatus acusticus externus
- but not earlobe, Helix or Concha

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Vagus somatosensory evoked potentials

modifiable
By local anesthesia
amplitude of the VSEP
reduced

Vagus somatosensory evoked potentials

reproducible
- intraindividual (immediately and after 2 weeks)
- interindividual (averaging possible)

<table>
<thead>
<tr>
<th></th>
<th>intraclass-correlation</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C4-F4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P1</strong></td>
<td>0.70 (0.41 - 0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>N1</strong></td>
<td>0.59 (0.19 - 0.79)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>P2</strong></td>
<td>0.42 (-0.13 - 0.70)</td>
<td>0.055</td>
</tr>
<tr>
<td><strong>Fz-F4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P1</strong></td>
<td>0.89 (0.78 - 0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>N1</strong></td>
<td>0.91 (0.82 - 0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>P2</strong></td>
<td>0.74 (0.47 - 0.87)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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Vagus somatosensory evoked potentials

modifiable
- stimulation intensity:
  - 5 mA – no useful VSEP
  - 8 mA – VSEP
  - 10 mA – VSEP, but painful

- study with different stimulation frequencies is under way

Vagus somatosensory evoked potentials

Aim: Optimizing of the parameters of stimulation

- Duration of stimulus:
  - 0.1 ms vs. 0.05 ms
- Interstimulus interval:
  - 0.5 Hz vs. 1 Hz vs. 1.33 Hz
- Intensity:
  - 8 mA vs. 6 mA
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Vagus Somatosensory Evoked Potentials – in special groups of patients
VSEP in elderly

VSEP in healthy elderly in contrast to younger healthy controls

Increasing age – reduced latency

Increasing age – similar amplitudes

Fallgatter AJ, Ehlis AC, Ringel TM, Herrmann MJ: Age effect on far field potentials from the brain stem after transcutaneous vagus nerve stimulation.
Int J Psychophysiol 2005;56:37-43
VSEP in Dementia: Alzheimer’s Disease

VSEP in AD in contrast to healthy elderly:

Latency: significantly reduced

Amplitudes: no reduction

VSEP in Dementia: Alzheimer‘s Disease

Every peak similarly delayed

## VSEP in Dementia: Mild Cognitive Impairment and Alzheimer’s Disease

<table>
<thead>
<tr>
<th></th>
<th>AD</th>
<th>MCI</th>
<th>HC</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td><strong>Number of subjects</strong></td>
<td>9</td>
<td>7</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td><strong>Age in years</strong></td>
<td>75.9 ± 8.2</td>
<td>69.0 ± 7.4</td>
<td>70.4 ± 6.2</td>
<td>0.087</td>
</tr>
<tr>
<td><strong>Gender (m/f)</strong></td>
<td>2/7</td>
<td>5/2</td>
<td>12/11</td>
<td>0.130</td>
</tr>
<tr>
<td><strong>Education in years</strong></td>
<td>8.7 ± 1.4</td>
<td>9.3 ± 3.4</td>
<td>10.2 ± 2.7</td>
<td>0.318</td>
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<tr>
<td><strong>MMST</strong></td>
<td>21.8 ± 3.2</td>
<td>25.9 ± 1.7</td>
<td>29.1 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>CERADplus mean</strong></td>
<td>-1.4 ± 0.34</td>
<td>-0.68 ± 0.62</td>
<td>0.57 ± 0.43</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Identifying Alzheimer's disease earlier and easier: new method on the horizon?

VSEP in Dementia: Mild Cognitive Impairment and Alzheimer’s Disease

<table>
<thead>
<tr>
<th></th>
<th>HC</th>
<th>MCI</th>
<th>AD</th>
<th>HC-AD</th>
<th>HC-MCI</th>
<th>MCI-AD</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>p</td>
<td>p</td>
<td>p</td>
</tr>
<tr>
<td>C4-F4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>1.83 ± 0.46</td>
<td>2.59 ± 0.29</td>
<td>2.28 ± 0.40</td>
<td>0.009</td>
<td>0.001</td>
<td>0.162</td>
</tr>
<tr>
<td>N1</td>
<td>3.74 ± 0.73</td>
<td>4.25 ± 0.69</td>
<td>3.86 ± 0.40</td>
<td>0.646</td>
<td>0.087</td>
<td>0.256</td>
</tr>
<tr>
<td>P2</td>
<td>5.29 ± 0.89</td>
<td>5.67 ± 0.72</td>
<td>6.33 ± 0.98</td>
<td>0.005</td>
<td>0.324</td>
<td>0.151</td>
</tr>
<tr>
<td>Fz-F4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>2.46 ± 0.73</td>
<td>2.31 ± 0.81</td>
<td>2.74 ± 0.46</td>
<td>0.316</td>
<td>0.628</td>
<td>0.233</td>
</tr>
<tr>
<td>N1</td>
<td>4.00 ± 0.92</td>
<td>4.65 ± 1.51</td>
<td>5.12 ± 0.57</td>
<td>0.006</td>
<td>0.136</td>
<td>0.347</td>
</tr>
<tr>
<td>P2</td>
<td>5.51 ± 0.97</td>
<td>5.94 ± 1.29</td>
<td>6.97 ± 0.96</td>
<td>0.001</td>
<td>0.339</td>
<td>0.057</td>
</tr>
</tbody>
</table>

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VSEP in Dementia: Mild Cognitive Impairment and Alzheimer‘s Disease


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VSEP in Dementia: Mild Cognitive Impairment and Alzheimer's Disease

VSEP in Dementia: Mild Cognitive Impairment and Alzheimer‘s Disease

VSEP in neurodegenerative disease: Parkinson‘s Disease

Other diseases with affection of the brain stem: similar changes:
- M. Parkinson
- Encephalomyelitis disseminata

Identifying Alzheimer’s disease earlier and easier: new method on the horizon?

VSEP in Dementia: Vascular Dementia

Other etiologies of dementia without explicit ascending course from brain stem: No characteristic changes of the VSEP

Example: vascular dementia

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VSEP in Dementia: Frontotemporal Dementia

FTD - Ktr. (C4-F4, n=5)
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Studies under way: longterm course of VSEP in neurodegenerative diseases

Hypothesis: Intraindividual hyperproportional delay of latency and also a reduction of amplitude is a correlate of a neurodegenerative progress
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Further studies and previews
Does (f)MRT correlate with VSEP?

Two fMRI-study combined with transcutaneous stimulation of N. Vagus:
- reduced activity of the BOLD-signal in the Gyrus temporalis superior and medius – not replicated
- Left prefrontal cortex, left thalamus, Locus coeruleus as projection areas have an increased activity

Pending structural and also functional imaging of the brainstem including Nuclei of the N. Vagus – demonstration of the changes in VSEP possible?

Identifying Alzheimer’s disease earlier and easier: new method on the horizon?

TREND-study

Tübinger evaluation
Risk factors for
Early detection of
Neurodegeneration
Identifying Alzheimer’s disease earlier and easier: new method on the horizon?

CERAD (part 1)
- Test of colour vision
- Test of smelling
- Neurological examination
- Blood testing

CERAD (part 2)
- Near-infrared Spectroscopy

Transcranial sonography (TCS)
- Extracran. Duplex ultrasound: Intima-Media-Thickness
- Test of autonomic function

Test of fine motor skills
- Analysis of gait
- Waist to hip ratio
- General anamnesis
- Anamnesis Delirium
- Anamnesis RBD
- Anamnesis Depression

Vagus Somoatosensory Evoked Potentials

Depression
- 120

Hyposmia
- 164

REM sleep behaviour disorder
- 73

Waist to hip ratio
- 77

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Near-infrared Spectroscopy

Near-infrared light (approx. 650-950 nm) penetrates biological issue
Identifying Alzheimer's disease earlier and easier: new method on the horizon?

Near-infrared Spectroscopy

Near-infrared light (650 – 950 nm)
Near-infrared Spectroscopy

Emitters and detectors (= optodes) are fixed at a cap
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Near-infrared Spectroscopy

Principle of NIRS: different absorption of NIR light by oxygenated and deoxygenated blood
Identifying Alzheimer’s disease earlier and easier: new method on the horizon?

Neurovascular coupling

- Increase of circulation in activation of areas
- Local and temporal correlation of neuronal activity and vascular response
- Overshooting response: more oxygenated blood than necessary = Hyperoxygenation
- Increase of oxygenated hemoglobin
- Decrease of deoxygenated hemoglobin
- = Blood Oxygenation Level Dependent (BOLD) effect
Cognitive task during NIRS

Verbal fluency task

- letter task: pronounce as many nouns as possible beginning with the same letter, for example „F“ (30 s)
- category task: pronounce as many nouns as possible belonging to the same category, for example animals or flowers (30 s)
- control task: recital of week days (30 s)
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Verbal Fluency Task

Controls

AD

Decreased activity of the frontal lobe during verbal fluency in AD
Identifying Alzheimer's disease earlier and easier: new method on the horizon?

Visuo-constructional Task
Benton line-orientation Task

Orientation of the lines

Colour of the lines (=control task)

test line

Task lines
Identifying Alzheimer's disease earlier and easier: new method on the horizon?

Decreased activity of the parietal lobe during visuo-construction in AD
Near-infrared Spectroscopy

TREND-cohort: correlation of brain activity measured by NIRS and age (healthy elderly, maximum MCI, no Parkinson)

TREND-study

Longitudinal study design:

Baseline examination 2009/2010 – 700 participants

1. Follow up examination 2011/12 – 1200 participants – newly integrated: VSEP and NIRS

- in April 2012 1. follow up finished
- Analysis of the data including NIRS and VSEP is pending
- large project for our team for the next months
Identifying Alzheimer's disease earlier and easier: new method on the horizon?

Summary VSEP

feasibility of the method
- simply applicable
- inexpensive
- no side effects
- reproducible
- no active cooperation necessary
- no visual or auditory abilities necessary
- time saving: preparation - 10-15 min., stimulation 3 min.
- ideal for screening
Identifying Alzheimer's disease earlier and easier: new method on the horizon?

Summary VSEP II

Latency increased, but no decreased amplitude
• with increasing age

• in neurodegenerative diseases:
  • Alzheimer’s Disease
  • Mild cognitive impairment
  • Parkinson’s Disease
  • Encephalomyelitis disseminata

• but not in dementia of other etiology
  • Vascular dementia
  • Frontotemporal dementia
Thanks to all

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Dipl. Psych. Sabrina Schneider
Dipl. Psych. Lena Ernst
Dipl. Psych. Agnes Kroczek
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Betti Schopp, MTAF
Lisa-Marie van der Luppe

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Prof. D. Berg and the TREND-team, Dept. of Neurology University Tuebingen
Thank you for your attention
Identifying Alzheimer's disease earlier and easier: new method on the horizon?

**AD/MCI/HC: left side stimulation (C3-F3)**

No significant group differences
AD/MCI/HC: right side stimulation (FZ-F4)