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Bilateral Peripheral Vestibular System Impairment

Gary Jacobson, Devin McCaslin, Kelsey Hatton
Part #1 – Introduction to the topic
Learning Objectives

• List the most common causes of bilateral vestibular system impairment.
• Explain the epidemiological aspects of bilateral peripheral vestibular system impairment.
• Describe the differential effect of mild cognitive impairment and Alzheimer's disease on semicircular canal and otolith end organ function.
• Explain the effect of profound peripheral vestibular system impairment on the hippocampus.

Introduction to: Bilateral Peripheral Vestibular System Impairment

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Vanderbilt University Medical Center
Introduction/Epidemiology
Bilateral Vestibular Hypofunction & Failure

- BVH/BVF occurs in ~7% of outpatients in a dizziness clinic
- Characterized by bilateral loss of nerve or end organ function, or both

Recognizing the Symptoms of BVF
van de Berg et al. (2015)

- 4 different clinical pictures (does not require patient to have hearing loss, tinnitus or vertigo)
  - Recurrent vertigo with BVH – vertigo spells over years followed by symptoms of bilateral BVH
  - Slowly progressive BVH – gradual onset of BVF symptoms without spells of vertigo
  - Rapidly progressive BVH – sudden onset of symptoms with or without vertigo e.g. ototoxicity, autoimmune origins
  - BVH with other neurological deficits – e.g. cerebellar ataxia
Symptoms of BVH/BVF
van de Berg et al. 2015

• Oscillopsia
• Imbalance
• Visual vertigo
• Cognitive impairments
• Psychological or psychiatric impairments
• Neurological impairments
• Autonomic system impairments

Symptoms of BVH
van de Berg et al. 2015

• Oscillopsia
  – Affects 25%-86% of patients with bilateral vestibular impairments.
  – Loss of VOR causes stationary objects to move on the retina during high frequency head movements. Produces “retinal smear” that normally triggers compensation in unilaterals
    • Patients may think they have a visual impairment because vision is blurry with head movement
Symptoms of BVH  
van de Berg et al. 2015

• Imbalance:
  – The VSR is impaired, because gravity detection is impaired, which reduces the patient’s ability to execute fast postural corrections.
  – Also, the central balance system substitutes vision and proprioception for the vestibular loss which causes unsteadiness or imbalance when these remaining senses are challenged (darkness, uneven surfaces or when visual field is “active”)

• Visual vertigo:
  – Describes patients with BVF who have become reliant on vision for orientation.
  – This produces unsteadiness/disorientation in active visual environments (e.g. scrolling text on a computer, crowds, windshield wiper motion)
Symptoms of BVH
van de Berg et al. 2015

• Cognitive deficits (will address further later):
  – Difficulty concentrating (brain fog), extreme fatigue (due, in part, to state of continuous vigilance to remain steady).
  – Patients find it difficult to “talk while walking.”
    • That is, when given a cognitive task during ambulation, patients will “stop walking when talking.”

• Psychological or psychiatric symptoms:
  – Chronic unsteadiness and impaired ADLs is a source of anxiety and depression in dizzy/unsteady/vertiginous patients
  – Anterior hippocampus is critically involved in emotional processes
Symptoms of BVH
van de Berg et al. 2015

• Neurological symptoms:
  – BVF also can be associated with neurodegenerative diseases e.g. spinocerebellar ataxia, CANVAS (cerebellar ataxia, neuropathy, vestibular areflexia syndrome).
  • Up to 39% of bilateral patients may have a neurological disorder.

• Autonomic symptoms:
  – Vestibulosympathetic reflex – Vestibular system projects to sites important for regulation of blood pressure and heart rate, and to sites that mediate affective and emotional aspects of vestibulo-autonomic function.
  – BVF can lead to orthostatic hypotension, panic
Self-report dizziness handicap in patients with bilateral failure

Recognizing the Impact of BVH
van de Berg et al. (2015)

- DHI scores show:
  - 43% of patients with moderate handicap
  - 41% of patients with severe handicap,

- In childhood bilateral vestibular hypofunction:
  - Can delay development of walking
  - Can create learning difficulties
Self-report dizziness handicap in patients with bilateral hypofunction vs failure
Jacobson and Calder (2000)

Quantitative assessment of patients with bilateral failure (tools, frequency spectrum, results)
Determination of Bilateral Peripheral Failure

• Era dependent. It was possible that a patient diagnosed with BVF in the 1960’s and 1970’s might not have been completely true
  – In 1960’s only caloric testing existed
  – In 1970’s rotational testing provided a means of obtaining information about “mid-frequencies”
  – VEMP’s were discovered in the 1990’s and 2000’s
  – vHIT was developed in the 2000’s to provide more ecologically-valid stimulus

Laboratory Testing
(Expected findings in BVL)

• Caloric test (.003 Hz) – no caloric response to ice water
• Chair test
  – Step test –abnormal low gain, and reduced TC
  – Sinusoidal harmonic acceleration (SHA) - .01, .02, .04, .08, .16, .32 Hz – decrease/absent gain, abnormal phase leads
  • Cross check for caloric test
• vHIT – reduced gain, with overt/covert saccades
• oVEMP – reduced/absent (although often residual function exists)
• cVEMP – reduced/absent (although often residual function exists)
Causes of BVF

- Ototoxicity
- Ideopathic (including autoimmune, and genetic)
- Meniere’s Syndrome (bilateral)
- Meningitis
- Infectious labyrinthitis (bacterial, viral, fungal)
- NF2
- Bilateral vascular occlusion
- Cogan syndrome: (autoimmune d.) rare rheumatic disorder characterized by recurrent inflammation of the cornea and fever, fatigue, weight loss, episodes of dizziness and hearing loss
- Tumors of the temporal bone
- Otosclerosis
- Head injury
- Radiation therapy
- Aging

Potential Etiologies – Bilateral hypofunction

Prevalence and Incidence - BVH

• Typical BVH guidelines:
  – Functional impairment revealed by laboratory testing
  – Generally in reference to the status of the lateral semicircular canals
  – Leads to vestibulo-ocular or vestibulo-spinal reflex impairments, altering ability to maintain stable gaze and posture

• Classical symptoms:
  – oscillopsia, chronic disequilibrium, postural instability

• Estimates gathered through specialty balance clinics may not provide a fair representation of bilateral vestibular hypofunction among the general population due to economic and health barriers

Prevalence and Incidence - BVH


• Multiple components:
  1) establishing validity of questions used to identify vestibular hypofunction
  2) utilize data from a large national health survey to identify patients with bilateral vestibular hypofunction
  3) examine other variables and symptoms reported by BVH respondents

GOAL: estimate the prevalence of BVH
1: Establish BVH questions

- Using laboratory examinations and questionnaire, are BVH and UVH patients significantly different?
- 12 documented BVH
  - Ice calorics yielded < 5 degrees/sec total SPV
  - 5 ototoxicity, 1 Meniere’s, 1 head/neck trauma, 5 unknown cause
- 12 documented UVH for longer than 1 year
  - Ice calorics yielded < 5 degrees/sec SPV impaired ear
  - 12 patients with unilateral Meniere’s disease that had already undergone intra-tympanic gentamicin injection
- 13 respondents with no inner ear pathology or reported dizziness

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlate study to determine construct validity of the bilateral vestibular hypofunction case definition.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most answer ‘yes’ to all of the following:</th>
<th>BVH (12)</th>
<th>UVH (12)</th>
<th>Control (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness or balance problems in last 12 months?</td>
<td>12 (100%)</td>
<td>10 (83%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Feel off/balance or unsteady</td>
<td>12 (100%)</td>
<td>10 (83%)</td>
<td>2 (15%)</td>
</tr>
<tr>
<td>Have difficulty walking in the dark</td>
<td>12 (100%)</td>
<td>7 (58%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Have difficulty walking on uneven surfaces</td>
<td>12 (100%)</td>
<td>3 (25%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Become off/balance when moving your head</td>
<td>12 (100%)</td>
<td>1 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Drifting to the side when trying to walk straight</td>
<td>12 (100%)</td>
<td>1 (8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Problem defined as at least a ‘big problem’</td>
<td>12 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Duration of symptoms of at least 1 year</td>
<td>11 (92%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Results of a correlative validation of 31 subjects who were not recruited in the 2001 NHIS Balance Supplement. Values are cumulative counts of remaining respondents that used the case definition for confirmed bilateral vestibular hypofunction (BVH), unilateral vestibular hypofunction (UVH), and for those with an history of dizziness or balance complaints.
1: validity of BVH question findings

- 12 BVH and 12 UVH combined reported
  - 92% “feeling off balance or unsteady”
  - 67% “having difficulty walking in the dark”
  - 58% “drifting to the side when trying to walk straight”,
  - 42% “difficulty walking on uneven ground” and “blurred vision during head movements”
- 12 documented BVH
  - Significantly more likely to rate problems as “big” or “very big” than patients with UVH and controls
  - Significantly more likely to report symptoms “≥ 1x daily” or “almost always” than patients with UVH and controls

2: Large survey with BVH questions

- National Health Interview Survey (NHIS)
- Annually administered by the US Census Bureau
- Large sample size: 74236 respondents
- No follow up or contact following initial participation
- Activities of Daily Living (ADL) and social limitation questions are routinely posed
- In 2008 – supplemental dizziness and balance questions administered
  - 21781 respondents completed the supplement
2: NHIS responses for BVH

- In past 12 months, 3411 persons reported one of the following:
  - Problem with dizziness, balance, vertigo, floating, or tilting sensations
  - Lightheaded without motion, blurring of vision with head movement
  - Feeling as if you are going to pass out or faint

- BVH required positive answers for all of the following:
  - Blurring of vision with head movement, off-balance or unsteady, drift when trying to walk straight, difficulty walking in the dark or difficulty walking on uneven ground/surfaces
  - Dizziness also had to be rated as at least a big problem with duration of dizziness > 1 year

- Must respond negatively for:
  - Spinal injury, stroke, movement disorders, muscular dystrophy, multiple sclerosis, AREDS, diabetic retinopathy

3: Other variables for NHIS BVH

- Functional limitations: Very difficult or could not perform
  - 9 activities of daily living questions
  - Walk 400m, walk up 10 steps no rest, stand for 2 hours, sit for 2 hours, stoop bend and kneel, reach overhead, grasp small objects, lift and carry up to 4.5kg, push & pull large objects

- Social limitations: Very difficult or could not perform
  - 3 social activity questions
  - Go out to things like shopping/movies/sporting events, participate in social activities such as visiting friends/attending clubs or meetings-going to parties, do things to relax at home or for leisure
3: other variables for NHIS BVH

- Equipment needs:
  - 1 question
  - Do you have any health problem that requires you to use special equipment such as a cane/wheelchair/special bed/special telephone

- Falls:
  - 2 questions
  - Falls sustained within 1-5 years, injury sustained due to falls

- Other queries:
  - Dizziness characterization, severity, duration, frequency, mitigating/provoking factors, associated symptoms of dizziness
  - Use of balance aids, physical problems, psychological problems, health care, pharmacological management, other diagnoses, treatments offered, treatment outcomes, and absenteeism

3: related variables for NHIS BVH

- 12/21781 respondents fulfilled BVH requirements
  - reported a “big” impact with symptoms of blurring of vision, unsteadiness, drifting when walking, and walking difficulties in dark or on uneven surfaces for more than 12 months (unrelated to other CNS, vision, or muscular issues)

- Sex – females more likely to have BVH
- Race/ethnicity – Hispanic more likely to have BVH
- Age – older respondents more likely to have BVH
- Diagnoses – diabetes or depression more often seen with BVH
3: related variables for NHIS BVH

- Impairments – those with BVH more likely to experience functional, social, and physical impairment
  - Functional: 58% limited in ≥ 4 of 9 ADLs
  - Social: 39% limited in social activities
  - Physical: 67% fell within last year with 1/4 sustaining an injury from falling
    - BVH respondents have a 9.9x fold increase of falling compared to those just reporting dizziness, a 31x fold increase in nationwide average fall risk
  - Other: BVH patients had motion intolerance or limited/changed driving habits, 55% missed work or school, 75% were unemployed

3: treatments for NHIS BVH

- Treatments – 9/12 BVH survey respondents had completed treatment
  - 56% had completed physical therapy,
  - 33% altered diet,
  - 22% had tried head rolling maneuvers, massage therapy, herbal remedy
  - 11% had undergone head/neck surgery, chiropractic remedy, tried wearable magnets.
  - 75% saw no change or worsening of symptoms
  - Saw 5.6 health care professionals on average (SD: 2.9)
  - Only 25% felt health care professional helped with their dizziness
GOAL: Prevalence Estimation

• Dizziness: 14.8% of US adults over a 12 month period
  – 18% of female respondents, 11% of male respondents
  – 27.7% of those aged ≥ 75

• BVH based on history:
  – 12/21782 respondents
  – Estimated 28 of every 100000 US adults
  – 64046 US adults, 1.8 million adults worldwide
  – With more lax qualifications: Estimated 85 of every 100000
    US adults
    • 193369 US adults in 2008

Part #3

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Vanderbilt University Medical Center
Background
Alzheimer’s Disease

- Est. 5.1 million cases in 2015
- Vestibular loss is associated with a cognitive impairment (both animals and humans)
- Volume loss in those brain areas where these functions reside
- Impairments in visuo-spatial skills
  - Spatial memory
  - Spatial navigation

Background
Alzheimer’s Disease

- Visuo-spatial impairments occur frequently in dementia
- Wandering is a common symptom of AD
- Dementia may have several underlying causes
  - Vascular
  - Cerebral degeneration
Background
Mild Cognitive Impairment

- Highly morbid condition
- Prevalence increases with age
- Patients have difficulty with objective cognitive tasks
- Day-to-day functioning is intact
- Concomitant vestibular impairment may complicate dementia and may be associated with impairments in ADLs and place patients at increased risk of falls.

Background
Few studies have examined vestibular impairment in individuals with cognitive impairment

- Patients with AD have poorer postural control compared to normal elderly (Leandri et al. 2009)
- Abnormal cVEMPs in patients with cognitive impairments (Birdane et al. 2012)
Purpose of Investigation

• Comprehensively assess vestibular physiologic function in a well-characterized cohort of patients with AD and MCI

• Hypothesis: Patients with cognitive impairment will have poorer vestibular function compared to age-matched controls.

• Subjects with more advanced cognitive impairment will demonstrate a greater amount of vestibular impairment.

Methods

• Subjects recruited from Johns Hopkins Memory and Alzheimer’s Treatment Center (JHMATC)
  – N = 15 patients with mild cognitive impairment (MCI)
  – N = 32 with AD

• Inclusion criteria:
  – Age > 55 years
  – Diagnosis of MCI or AD (NIA/AD diagnostic criteria)
  – MMSE > 11 (cut-off for moderate-severe cognitive impairment)
  – Fluent in English
  – Ability to provide informed consent from participant or legal representative
  – Screened by physician who could determine whether subject was capable of performing tasks
Subject Characteristics

### Methods

- **Exclusionary criteria**
  - Previous history of vestibular disease
  - Unable to understand examination procedures
  - Unable to participate in study procedures because of physical conditions e.g.
    - Blindness
    - Poor neck range of motion
    - Cervical-spine instability

- **Age, sex and education-matched data was drawn from Baltimore Longitudinal Study on Aging (BLSA)**
  - BLSA is a prospective cohort study of participant volunteers aged 21-103 years in the National Institute on Aging Clinical Research Unit at Harbor Hospital in Baltimore, MD
Methods
VFT- cVEMP

- Patient supine, head elevated 30 deg. from horizontal
- Electrodes placed on SCM bilaterally (active) and at the sternoclavicular junction (reference), ground placed at the manubrium sterni
- EMG activity was filtered 20-2000 Hz
- Stimulus = 500 Hz tone burst 125 dB SPL presented monaural through head phones
- cVEMP was normalized for the magnitude of tonic EMG activity
- Data from the better ear was used for the analysis
- One subject’s data was eliminated because they could not follow directions

Methods
VFT - oVEMP

- Patient supine with head elevated 30 deg from horizontal
- Electrodes placed on cheek beneath the pupil 3 mm below the eye (active), placed 2 cm beneath the first electrode (reference), ground placed at manubrium sterni
- Ensured that both eyes could avert 20 degrees
- Head taps were delivered from a reflex hammer in the midline at the hairline 30% of the distance between the inion and nasion
- oVEMP amplitude of the better ear was used for analysis
- 2 subjects were eliminated because they could not follow directions
Methods
VFT - vHIT

- Performed in the plane of the right and left horizontal semicircular canals.
- Patient’s head was pitched downward 30 deg to place the horizontal canals in the plane of stimulation.
- Subjects fixed their gaze on a target 1.5 meters away.
- The head as moved 5-15 degrees (150-250 degrees)
- 10 samples in each direction
- VOR gain was quantified as eye velocity/head velocity
- Gains of < 80% usually are accompanied by refixation saccades and suggest a loss of peripheral vestibular function
- Six patients could not be tested

Results

- N = 47 patients (32% dx with MCI, 68% with AD)
- Mean age = 75 years (70% women)
- N = 94 controls
- Controls with higher MMSE than experimentals (mean = 28.6 controls, 25.7 MCI, 19.7 AD)
Results

• AD with:
  – ...higher prevalence of bilaterally absent cVEMP (50%) compared to controls (25%)
  – ...smaller cVEMP amplitude (.8 uV) compared to controls (1.3 uV)
  – ...smaller oVEMP amplitude (9.4 uV) compared to controls (13.7 uV)

• No significant difference between MCI group and controls in prevalence of vestibular impairment

Mean Vestibular Function for Controls vs MCI and AD

| TABLE 2. Mean vestibular function among controls and cognitive impairment categories |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | MCI (n = 15) | Controls (n = 30) | p    | AD (n = 32) | Controls (n = 64) | p    |
| Bilaterally absent cVEMPs      |              |                  |      |              |                    |      |
| Yes                           | 4 (26.7%)    | 7 (23.3%)        | 0.806|              |                      |      |
| No                            | 11 (73.3%)   | 23 (76.7%)       |      |              |                      |      |
| cVEMP amplitude in µV (SD)     | 1.7 (1.4)    | 1.2 (0.6)        | 0.175|              |                      |      |
| Bilaterally absent oVEMPs      |              |                  |      |              |                      |      |
| Yes                           | 4 (26.7%)    | 6 (20.0%)        | 0.612|              |                      |      |
| No                            | 11 (73.3%)   | 24 (80.0%)       |      |              |                      |      |
| oVEMP amplitude in µV (SD)     | 13.8 (5.2)   | 15.2 (7.3)       | 0.554|              |                      |      |
| Mean VOR gain (SD)            | 1.0 (0.1)    | 1.0 (0.2)        | 0.621|              |                      |      |

Data in boldface indicates statistical significance.
µV indicates microvolts; AD, Alzheimer’s disease; cVEMPs, cervical vestibular-evoked myogenic potentials; MCI, mild cognitive impairment; oVEMPs, ocular vestibular-evoked myogenic potentials; SD, standard deviation; VOR, vestibular ocular reflex.
Results

- Subjects with bilaterally absent cVEMP:
  - 3x increased odds of having AD (OR = 3.42; 95% CI = 1.32 – 8.91).

- Subjects with larger oVEMP amplitude
  - 1x decreased odds of having AD (OR = .92; 95% CI = .85-.99)

- vHIT: VOR gain did not significantly differ by cognitive impairment category, including AD

Logistic regression for the odds of cognitive impairment associated with vestibular impairment

<table>
<thead>
<tr>
<th>Cognitive Impairment</th>
<th>MCI OR</th>
<th>95% CI</th>
<th>p</th>
<th>AD OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral absent cVEMP</td>
<td>1.20</td>
<td>0.28–5.03</td>
<td>0.807</td>
<td>3.42</td>
<td>1.32–8.91</td>
<td>0.011</td>
</tr>
<tr>
<td>cVEMP amplitude in µV</td>
<td>1.97</td>
<td>0.80–4.87</td>
<td>0.142</td>
<td>0.28</td>
<td>0.09–6.85</td>
<td>0.638</td>
</tr>
<tr>
<td>Bilateral absent oVEMP</td>
<td>1.59</td>
<td>0.31–8.17</td>
<td>0.581</td>
<td>1.97</td>
<td>0.38–3.94</td>
<td>0.921</td>
</tr>
<tr>
<td>oVEMP amplitude in µV</td>
<td>0.97</td>
<td>0.85–1.09</td>
<td>0.581</td>
<td>0.82</td>
<td>0.88–5.99</td>
<td>0.036</td>
</tr>
<tr>
<td>Mean VOR gain</td>
<td>0.33</td>
<td>0.01–31.47</td>
<td>0.949</td>
<td>0.80</td>
<td>0.03–13.28</td>
<td>0.720</td>
</tr>
</tbody>
</table>

Data in boldface indicates statistical significance.

µV indicates microvolts; AD, Alzheimer's disease; CI, confidence interval; cVEMP, cervical vestibular-evoked myogenic potentials; MCI, mild cognitive impairment; oVEMP, ocular vestibular-evoked myogenic potentials; VOR, vestibular ocular reflex.

*Adjusted for age, sex, and education. Reference category is the age, sex, and education-matched reference group.
Discussion

- Reported a significantly higher prevalence of vestibular loss among individuals with dementia compared to age-matched controls
- Impairments **did affect** saccule and utricle compared to controls
- Impairments **did not** affect semicircular canals compared to controls
- “…we observed that individuals with AD but not mild cognitive impairment, were more likely to have vestibular loss relative to age-matched controls.”

Discussion

- Vestibular system sends projections to cortical areas involved with memory and spatial orientation including the hippocampus
- Projections form a neural basis for the association between vestibular and cognitive function.
- Stimulation of vestibular system in animals results in increased firing in hippocampal neurons
- Animals with vestibular lesions:
  - Show a disruption of theta rhythm (thought to encode spatial information)
  - Perform poorly on spatial navigation tasks
Discussion

• Hippocampal atrophy is pathological hallmark of AD
• Connections between vestibular system and hippocampus may underlie the association between vestibular loss and dementia
• Previous studies:
  – Leandri et al. progressive increase in anterior-posterior sway for controls, MCI and AD subjects
  – Birdane et al. subjects with any degree of cognitive impairment demonstrated lower mean cVEMP amplitudes compared to controls

Discussion

• No association between the VOR and cognitive function.
• Neurons in the vestibular nucleus involved with the VOR are distinct from other vestibular neurons since they do not ascend to the thalamus and project cortically
• Saccular stimulation leads to widespread cortical activation including the posterior insular cortex, inferior parietal cortex, intraparietal sulcus, temporoparietal junction
  – All are involved in cognitive processing
• Disruption of in the peripheral vestibular projections to the cortex may underlie the association between cognition and otolith function
• Otolith-cervical and otolith-ocular projections that underlie the VEMP responses are distinct from the otolith-cortical projections that may account for the association between otolith and cognitive function
Summary

“Our work confirms and extends emerging evidence of an association between vestibular loss and cognitive decline. Further investigation is needed to determine the causal direction for the link between peripheral vestibular loss and cognitive impairment. Identification of a possible modifiable risk factor such as vestibular loss for cognitive impairment could lead to interventions to help slow the progression of dementia and reduce the risks of postural instability and falls in this already vulnerable population.”

References


Vestibular Loss Causes Hippocampal Atrophy and Impaired Spatial Memory in Humans

Thomas Brandt, Franz Schautzer, Derek A. Hamilton, Roland Bruning, Roger Kalla, Cynthia Darlington, Paul Smith, and Michael Strupp

Brain, (128): 2732-2741, 2005
Background

- Input from the vestibular system is important for navigation and spatial memory in animals.
- The hippocampus has been suggested to play a key role in the tasks.
- Electrophysiological studies from the 1990s showed that vestibular stimulation could modulate the activity of ‘place cells’ in the hippocampus.

O’Mara et al., 1994; Gavrilov et al., 1995

Hippocampus
“Sea Horse”
Hippocampus and Parahippocampus

- Hippocampal and parahippocampal cortices create cognitive maps (cognitive map = neural representation of the environment).
- Construction of these maps is based on:
  - place cells,
  - border cells,
  - head direction cells and
  - grid cells
  - that are found in the hippocampal formation and parahippocampus

Hitier et al. 2014

Background

- Reports have suggested that spatial learning deficits in animals after vestibular lesions or stimulation are linked to changes in neural wiring critical for navigation and place learning.
- Location-related firing of ‘place cells’ in the hippocampus were abolished in rats after bilateral labyrinthectomy.

Stackman et al., 2002
Purpose of the Investigation

• Can MRI volumetry show morphological changes in the hippocampus of BVL patients?

• Are the BVL-related deficits in spatial memory and navigation selective or associated with general memory deficits?

Methods

• Ten patients (four women, six men) with BVL and ten sex and age-matched controls with no known neurological history participated in the study.

• All experimental patients had undergone a bilateral vestibular nerve section 5–10 years before the test and subsequently had a complete BVL.
Methods

• T2-weighted images were obtained in the oblique coronal orientation perpendicular to the long axis of the hippocampus.

• Also assessed:
  – Intelligence
  – Memory and attentional concentration
  – Spatial learning and spatial memory

Patients with BVF Demonstrate Impaired Spatial Memory

• Spatial memory:
  – is responsible for recording information about one’s environment and its spatial orientation.
  – is required to navigate around a familiar city, just as a rat's spatial memory is needed to learn the location of food at the end of a maze.
  – can be short-term or long-term.

The Morris water navigation task is a classic test for studying spatial learning and memory in rats:
Morris Water Navigation Task

- Parameters assessed are:
  - Search Latency
  - Path Length
  - Dwell time

vMWT and Variants in BVH

- An example of a homeward path taken by a BVD rat and a sham control rat at 14 months post-op. During a foraging task in darkness in which animals had been trained to forage for food and navigate their way back to a home base.

Smith PF, Zheng, Y, 2013
Design and Procedure

• Phase I - participants completed five hidden platform training blocks, each consisting of four trials.
• Phase II - consisted of a single 45 s probe trial during which the platform was removed from the environment.
• Phase III - condition provided a control task that did not require spatial processing, which is intact in individuals with spatial navigation impairment.

Virtual (human) Morris Water Maze Test

https://www.youtube.com/watch?v=v1EPF3YGaHo
http://www.frontiersin.org/files/Articles/25389/fpsyg-03-00304-HTML/image_m/fpsyg-03-00304-g001.jpg
Castell and Larios
Results

- MRI volumetry revealed a 16.91% decrease in total hippocampal volume in the BVL patients relative to controls.

### Table 1 Mean hippocampal, GM, WM, CSF and whole-brain volume (± SD) measured by MRI volumetry in NF2 patients and controls

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<tr>
<th></th>
<th>Control (male)</th>
<th>Control (female)</th>
<th>BVL (male)</th>
<th>BVL (female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right HPC (cm³)</td>
<td>2.67 (0.14)</td>
<td>1.55 (0.23)</td>
<td>2.31 (0.40)</td>
<td>2.02 (0.24)</td>
</tr>
<tr>
<td>Left HPC (cm³)</td>
<td>2.91 (0.26)</td>
<td>1.45 (0.31)</td>
<td>2.13 (0.47)</td>
<td>2.06 (0.15)</td>
</tr>
<tr>
<td>Total HPC (cm³)</td>
<td>5.59 (0.38)</td>
<td>4.98 (0.52)</td>
<td>4.44 (0.33)</td>
<td>4.08 (0.38)</td>
</tr>
<tr>
<td>Gray matter (cm³)</td>
<td>544.32 (21.38)</td>
<td>507.40 (10.94)</td>
<td>640.79 (38.64)</td>
<td>503.64 (60.01)</td>
</tr>
<tr>
<td>White matter (cm³)</td>
<td>683.33 (100.67)</td>
<td>596.63 (40.47)</td>
<td>690.80 (83.22)</td>
<td>532.29 (68.26)</td>
</tr>
<tr>
<td>Whole brain (GM + WM, cm³)</td>
<td>1281.65 (103.7)</td>
<td>1171.01 (65.60)</td>
<td>1339.69 (179.8)</td>
<td>1035.94 (99.94)</td>
</tr>
<tr>
<td>CSF (cm³)</td>
<td>170.16 (27.11)</td>
<td>165.23 (20.20)</td>
<td>240.74 (43.81)</td>
<td>197.60 (20.89)</td>
</tr>
<tr>
<td>Right HPC/whole brain</td>
<td>0.209 (0.013)</td>
<td>0.211 (0.021)</td>
<td>0.174 (0.036)</td>
<td>0.195 (0.015)</td>
</tr>
<tr>
<td>Left HPC/whole brain</td>
<td>0.228 (0.009)</td>
<td>0.190 (0.038)</td>
<td>0.117 (0.034)</td>
<td>0.199 (0.011)</td>
</tr>
<tr>
<td>Total HPC/whole brain</td>
<td>0.437 (0.032)</td>
<td>0.408 (0.036)</td>
<td>0.311 (0.051)</td>
<td>0.394 (0.027)</td>
</tr>
</tbody>
</table>

HPC, hippocampus. *Measures were not obtained or could not be composed for four participants (3 BVL patients and 1 control).
Results

• There was not a significant difference in men vs. women for hippocampal measures with whole-brain volume (only four female patients).

• Table 1 indicates that BVL may have had a larger impact on hippocampal volume in female experimental patients.

Spatial Memory Results

• BVL patients took more time and longer paths to navigate to the platform than controls.

Table 3 Data for VMWT probe trial as percent time spent in the four platform quadrants (means, SEM)

<table>
<thead>
<tr>
<th></th>
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<th>BVL (male)</th>
<th>BVL (female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE (plat)</td>
<td>44.4% (6.7)</td>
<td>40.9% (6.9)</td>
<td>35.5% (5.3)</td>
<td>12.8% (4.9)</td>
</tr>
<tr>
<td>SE</td>
<td>31.1% (8.1)</td>
<td>17.3% (8.9)</td>
<td>20.2% (7.3)</td>
<td>41.5% (5.4)</td>
</tr>
<tr>
<td>SW</td>
<td>13.3% (5.5)</td>
<td>7.6% (5.9)</td>
<td>17.1% (6.4)</td>
<td>21.9% (5.3)</td>
</tr>
<tr>
<td>NW</td>
<td>13.3% (5.5)</td>
<td>34.2% (1.3)</td>
<td>17.1% (6.4)</td>
<td>23.9% (6.3)</td>
</tr>
</tbody>
</table>

NE, northeast; SE, southeast; SW, southwest; NW, northwest.
Discussion

• This study supports the concept that acquired chronic loss of vestibular function can result in hippocampal atrophy.

• The pattern of means for the probe trial measures in the VMWT closely matched the pattern of hippocampal volumes observed in the patient and control groups.

Discussion

• The study further suggests that vestibular and visual cues are critical for spatial navigation.

• A continuous accurate updating of the location and motion of the individual within a 3-dimensional environment requires input from both senses in order to navigate.
Discussion

• This study showing a link between BVL patients and bilateral hippocampal atrophy suggest that the hippocampus plays a key role in spatial aspects of memory processing for navigation.

• This study also demonstrated for the first time in humans that spatial navigation is dependent on preserved vestibular function, even when the subjects are stationary.

Questions