WHAT IS SLEEPINESS?
MICROSLEEP EPISODES IN THE BORDERLAND BETWEEN WAKEFULNESS AND SLEEP

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Dep. of Neurology
Inselspital
WHAT IS SLEEPINESS?
SLEEPINESS — UNDERLYING PHYSIOLOGICAL PROCESSES

Borbély, 1982; Daan et al., 1984; Borbély and Wirz-Justice, 1982
SLEEPINESS - WHAT CAUSES IT?

Factors influencing sleepiness

- Circadian factors
- Homeostatic factors
- Genetic and medical factors
- Environmental and social factors
SLEEPINESS - WHAT IS THE PREVALENCE?

Excessive daytime sleepiness:
Up to 27% of the general population

Kaneita et al., 2005; Pallesen et al., 2007; Ohayon, 2008; Swanson et al., 2011; Ohayon, 2012; Fatani et al., 2015
SLEEPINESS AND RELATED TERMS

- Hypersomnolence and sleepiness
- Fatigue and tiredness
- Neurological and internal diseases
- Sleep apnea, restless legs, and parasomnias
- Sleep deficiency
- Chronic fatigue syndromes
- Idiopathic hypersomnia
- Narcolepsy
- Insomnia and tiredness
- Non-organic hypersomnia
SLEEPINESS - HOW CAN IT BE ASSESSED?

Causes of sleepiness

Consequences of sleepiness

Chervin and Guilleminault, 1995
SLEEPINESS - HOW CAN IT BE ASSESSED?

Assessments of sleepiness

Subjective measures
- Questionnaires

Physiological measures
- Electroencephalography (EEG)

Behavioral measures
- Eyelid behavior, head nodding

Performance measures
- Reaction time, driving performance
MULTIPLE SLEEP LATENCY TEST (MSLT)
SLEEP SCORING CRITERIA

- Rechtschaffen and Kales
- American Academy of Sleep Medicine (AASM)
SLEEP SCORING CRITERIA
SLEEP SCORING CRITERIA

- Rechtschaffen and Kales
- American Academy of Sleep Medicine (AASM)
- AASM-defined sleep latency

![Graph showing sleep scoring criteria with time and EEG waves]
MAINTENANCE OF WAKEFULNESS TEST (MWT)

- Electroencephalogram (EEG) = brain waves
- Electrooculogram (EOG) = eye movements
- Electromyogram (EMG) = muscle tension
MICROSLEEP EPISODE (MSE) ASSESSMENT METHODS

1. Neurophysiological parameters

2. Behavioral parameters

3. Performance parameters

⇒ Minimal duration of 3-5 s
SLEEPINESS - POTENTIAL VALUE OF MSES

- Optimizing diagnostic process
- Optimizing treatment
- Optimizing fitness-to-drive assessment
- Including MSEs in sleepiness assessments
- Prevention of sleepiness-related accidents
SLEEPINESS - CONSEQUENCES

Sleepiness behind the wheel

- No: 65%
- Yes: 35%

Sleepiness-related traffic accidents

- Serious injuries or death: 17%
- Less serious injuries: 83%

Maycock, 1997; Nabi et al., 2006; Sagaspe et al., 2010; Gonçalves et al., 2015
How to improve the objective assessment of sleepiness?
1. Development of visual MSE scoring criteria
2. Development of automatic MSE detection method
3. Assessing automatically detected MSEs in relation to driving performance
OBJECTIVES (PAPERS)

1. Development of visual MSE scoring criteria
2. Development of automatic MSE detection method
3. Assessing automatically detected MSEs in relation to driving performance
OBJECTIVES
(PAPERS)

1. Development of visual MSE scoring criteria
2. Development of automatic MSE detection method
3. Assessing automatically detected MSEs in relation to driving performance
PAPER 1: MSES IN THE BORDERLAND BETWEEN WAKEFULNESS AND SLEEP


Sleep, 2019 (accepted)
## Previous Definitions of EEG-Based MSES

<table>
<thead>
<tr>
<th>Authors</th>
<th>Duration</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrison and Horne, 1996</td>
<td>3-14 seconds</td>
<td>Artifact-free episodes during which theta activity replace the waking alpha background rhythm</td>
</tr>
<tr>
<td>Tirunahari et al., 2003</td>
<td>3-15 seconds</td>
<td>Similar to N1</td>
</tr>
</tbody>
</table>
“BERN CONTINUOUS AND HIGH-RESOLUTION WAKE-SLEEP SCORING (BERN)” CRITERIA

- Duration:
  - 1 – 15 seconds

- Visual scoring of the occipital EEG-channels:
  - ‘Slowing’ visible, similar to N1
  - In ≥ 1 occipital EEG-channel

- Usually slow/rolling eye movements (EOG)

- Eyes closed ≥ 80% (face videography)
EYE CLOSURE CRITERION

Berger, 1929
MSE EXAMPLE

EOG - L
EOG - R
EEG - F4
EEG - F3
EEG - C4
EEG - Cz
EEG - C3
EEG - O2
EEG - O1
EMG - Chin

Time (30 s)
## STUDY POPULATION

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>76</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>50 males</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>45.62 [18.0-81.37] years</td>
</tr>
</tbody>
</table>
MAINTENANCE OF WAKEFULNESS TEST (MWT)
METHOD

- Scoring methods:
  - AASM criteria (30 s epochs)
  - BERN criteria (≥ 1 s)

- Scoring of data:
  - Around 2/3 of the recordings: scored by 2 scorers, differences resolved by discussion
  - Around 1/3 of the recordings: 1 scorer
METHOD

- **Main analysis:**
  - Only including recordings with $\geq 1$ MSE ($n = 42$)
  - Start of the test until the first epoch of AASM-defined sleep

- **Inter-scorer reliability:**
  - 5 recordings scored independently by 2 scorers
METHOD - ASSESSING PERFORMANCE INTER-SCORER RELIABILITY

- Specificity and accuracy:
  - Rely on correct detection of the majority of data points = number of true negatives (wakefulness)

- Sensitivity and precision:
  - Take true positives (MSEs) into account

- Cohen’s Kappa:
  - Agreement by chance taken into account
# RESULTS - INTER-SCORER RELIABILITY

<table>
<thead>
<tr>
<th>MSEs - BERN criteria</th>
<th>Sensitivity (%) (TP/TP+FN)</th>
<th>Specificity (%) (TN/TN+FP)</th>
<th>Cohen’s Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>74.1</td>
<td>98.1</td>
<td>0.77</td>
</tr>
</tbody>
</table>

TP= true positive, TN= true negative, FP= false positive, FN= false negative
## RESULTS - INTER-SCORER RELIABILITY

<table>
<thead>
<tr>
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<th>Cohen’s Kappa</th>
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<tr>
<td>MSEs - BERN criteria</td>
<td>0.77</td>
</tr>
<tr>
<td>N1-Rechtschaffen and Kales (Danker-Hopfe et al., 2004)</td>
<td>0.35</td>
</tr>
<tr>
<td>N1-Rechtschaffen and Kales (Danker-Hopfe et al., 2009)</td>
<td>0.41</td>
</tr>
<tr>
<td>N1-AASM scoring (Danker-Hopfe et al., 2009)</td>
<td>0.46</td>
</tr>
<tr>
<td>N1-AASM scoring (Magalang et al., 2013)</td>
<td>0.31</td>
</tr>
</tbody>
</table>
RESULTS - MSE CHARACTERISTICS

Number (#/patient)  Median duration (s/MSE)  Cumulative duration (s)
# RESULTS - COMPARISON BOTH SCORING METHODS

<table>
<thead>
<tr>
<th></th>
<th>MWT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency to 1st MSE (min)</td>
<td>16.02 [7.07-20.93]</td>
</tr>
<tr>
<td>Latency to AASM-defined sleep (min)</td>
<td>22.00 [11.00-27.50]</td>
</tr>
<tr>
<td>Testing</td>
<td>( p &lt; 0.01 )</td>
</tr>
</tbody>
</table>

(mean ± SD)
RESULTS - CORRELATION

Latency to first epoch of AASM-defined sleep (min)

Predicted AASM = 6.17 + 0.09 * MSE, p < 0.01
RESULTS - TIMING OF MSES

- MSEs

AASM-defined sleep

No AASM-defined sleep
BERN CRITERIA - LIMITATIONS

- Expertise needed
- Time-consuming
PAPER 2: AUTOMATIC DETECTION OF MSES WITH FEATURE-BASED MACHINE LEARNING

Skorucak J, Hertig-Godeschalk A, Schreier DR, Malafeev A, Mathis J, and Achermann P

Sleep, 2019 (accepted)
METHOD

- Included data:
  - Data of all patients (N=76)
  - Entire MWT trial
METHOD

- Machine learning using features:
  - Recurrent neural network
  - Random forest
  - Support vector machine

- Training \( n=53 \) and testing \( n=23 \) set
METHOD - FEATURE ENGINEERING
METHOD - ASSESSING PERFORMANCE

- Specificity and accuracy:
  - Rely on correct detection of the majority of data points
  - Hence, relying on number of true negatives (wakefulness)

- Sensitivity and precision:
  - Take true positives (MSEs) into account

- Cohen’s Kappa:
  - Agreement by chance taken into account
## RESULTS - PERFORMANCE OF THE ALGORITHMS

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Sensitivity (%) (TP/TP+FN)</th>
<th>Specificity (%) (TN/TN+FP)</th>
<th>Cohen’s Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent neural network</td>
<td>92.1</td>
<td>96.8</td>
<td>0.75</td>
</tr>
<tr>
<td>Random forest</td>
<td>89.4</td>
<td>97.0</td>
<td>0.75</td>
</tr>
<tr>
<td>Support vector machine</td>
<td>87.0</td>
<td>96.7</td>
<td>0.71</td>
</tr>
</tbody>
</table>

TP=true positive, TN=true negative, FP=false positive, FN=false negative
**COMPARISON OTHER STUDIES**

<table>
<thead>
<tr>
<th></th>
<th>Cohen’s Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSEs - BERN criteria, inter-scorer reliability (n=5)</td>
<td>0.77</td>
</tr>
<tr>
<td>MSEs - BERN criteria, automatic detection (n=23)</td>
<td><strong>0.75</strong></td>
</tr>
<tr>
<td>N1 - AASM scoring, automatic detection (Malafeev et al, 2018) (n=9)</td>
<td>0.40</td>
</tr>
<tr>
<td>N1 - AASM scoring, automatic detection (Stephansen et al, 2018) (n=793)</td>
<td>0.62</td>
</tr>
</tbody>
</table>
RESULTS - EXAMPLE AUTOMATIC DETECTION

LSTM - recurrent neural network, RF - random forest, SVM - support vector machine
RESULTS - EXAMPLE AUTOMATIC DETECTION

LSTM - recurrent neural network, RF - random forest, SVM - support vector machine
RESULTS - IMPORTANCE FEATURES
AUTOMATIC MSE DETECTION - OUTLOOK

- Mainly EEG-based
- Possible relation to performance?
PAPER 3: AUTOMATICALLY DETECTED MSES IN THE FITNESS-TO-DRIVE ASSESSMENT

Skorucak J, Hertig-Godeschalk A, Achermann P, Mathis J, and Schreier DR

*Frontiers in Neuroscience, 2019 (under review)*
## Study Population

<p>| | |</p>
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of participants</strong></td>
<td>18</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>8 females</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>23.3 ± 1.3 years</td>
</tr>
</tbody>
</table>
METHOD — DRIVING SIMULATOR (DSIM)
METHOD - DSIM

Standard deviation of lateral position (SDLP)

Off-road

-1000

Midline

0

+1000

Off-road
METHOD - STUDY PROCEDURE

18:00-23:00  
1X MWT AND 1X DSIM

FULL NIGHT OF SLEEP DEPRIVATION

07:00-12:00  
1X MWT AND 1X DSIM
PRIMARY AIM - MSES

MWT → MSEs

DSim

Driving performance
SECONDARY AIM - ALGORITHM PERFORMANCE

- Moderately sleepy patients
- Severely sleepy healthy participants
# RESULTS - ALGORITHM PERFORMANCE

<table>
<thead>
<tr>
<th>MSEs - BERN criteria, automatic detection</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Cohen's Kappa</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>70.0</td>
<td>93.3</td>
<td>0.66</td>
</tr>
<tr>
<td>Study Description</td>
<td>Cohen’s Kappa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>---------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSEs - BERN criteria, inter-scorer reliability (n=5 moderately sleepy patients)</td>
<td>0.77</td>
<td></td>
<td></td>
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<td>MSEs - BERN criteria, automatic detection (n=23 moderately sleepy patients)</td>
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</tr>
<tr>
<td>MSEs - BERN criteria, automatic detection (n=10 severely sleepy participants)</td>
<td>0.66</td>
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# RESULTS - MSE CHARACTERISTICS

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<th>Patients</th>
<th>Healthy participants</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>MWT</td>
<td>MWT</td>
</tr>
<tr>
<td><strong>Median MSE duration (s)</strong></td>
<td>3.5 [2.6-5.1]</td>
<td>4.50 [4.20-6.40]</td>
</tr>
<tr>
<td><strong>MSE rate (#/min)</strong></td>
<td>0.22 [0.08-0.51]</td>
<td>1.29 [0.73-1.83]</td>
</tr>
<tr>
<td><strong>Cumulative MSE duration (%)</strong></td>
<td>0.84 [0.22-2.32]</td>
<td>13.80 [9.35-22.53]</td>
</tr>
</tbody>
</table>

(mean ± SD)
## RESULTS - COMPARISON BOTH SCORING METHODS

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<td>MWT</td>
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<tr>
<td>Latency to 1st MSE (min)</td>
<td>16.02 [7.07-20.93]</td>
<td>2.43 [0.97-3.36]</td>
</tr>
<tr>
<td>Latency to AASM-defined sleep (min)</td>
<td>22.00 [11.00-27.50]</td>
<td>7.75 [5.00-20.50]</td>
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<tr>
<td>Testing</td>
<td>$p &lt; 0.01$</td>
<td>$p &lt; 0.01$</td>
</tr>
</tbody>
</table>

(mean ± SD)
RESULTS - TIMING OF MSEs
RESULTS - TIMING OF MSES

- MSEs
- AASM-defined sleep
- No AASM-defined sleep
- First off-road event
RESULTS - CORRELATIONS

MWT

MSEs

DSim
RESULTS - MSES AND DRIVING PERFORMANCE

The graph shows the variation of MSES, OFF, LP, and SDLP over time (in minutes). The data appears to fluctuate significantly across different time periods.
RESULTS - MSES AND DRIVING PERFORMANCE

[Graphs showing cumulative duration of different metrics over time (min)]
RESULTS - MSES AND DRIVING PERFORMANCE
RESULTS - MSES AND DRIVING PERFORMANCE
RESULTS - CORRELATIONS

- MWT
- MSEs
- DSim
- Driving performance
RESULTS - MSES AND DRIVING PERFORMANCE

Off-road events
(#)

Off-road events
(min)

SDLP

* p < 0.05
OVERALL DISCUSSION
SLEEPINESS AND ACCIDENTS

MSEs

Schreier et al., 2018
BERN SCORING CRITERIA

EEG-L
EEG-R
EEG-F4
EEG-F3
EEG-C4
EEG-Cz
EEG-C3
EEG-O2
EEG-O1
EMG-Chin

Time (30 s)
AUTOMATIC MSE DETECTION

LSTM - recurrent neuronal network, RF - random forest, SVM - support vector machine
MSES IN DIFFERENT TEST CONDITIONS

MWT

DSim
MSES VERSUS AASM

MWT

First MSE  AASM-defined sleep

DSim

First MSE  No AASM-defined sleep
MSES VERSUS AASM
MSES VERSUS AASM

AASM-defined sleep latency (min)

Time (hrs)

Bonnet et al., 2005
MWT AND DRIVING PERFORMANCE

MWT

MSEs

Driving performance
MWT AND DRIVING PERFORMANCE

Off-road events (mean #)

AASM-defined sleep latency

Philip et al, 2013
MSES AND DRIVING PERFORMANCE
MSES AND DRIVING PERFORMANCE

Boyle et al, 2008
INTER-INDIVIDUAL DIFFERENCES
HUMAN VERSUS COMPUTER
HUMAN VERSUS COMPUTER
LIMITATIONS

- Potential influence:
  - Diagnosis
  - Treatment

- Not all data visually scored:
  - Patients - Only 1 MWT trial visually scored
  - Healthy participants - only data of 10 visually scored
LIMITATIONS - EYE CLOSURE CRITERION
OUTLOOK - OTHER BRAIN REGIONS
OUTLOOK — OTHER BRAIN REGIONS

Cajochen et al., 2005
OUTLOOK - LOCAL MSES?

Huber et al, 2004
OUTLOOK

- MSEs in relation to:
  - Behavior: - eyelids
  - Performance: - reaction time
    - real-life driving/accidents
OVERALL CONCLUSION
CONCLUSION

➢ Developed the first visual scoring criteria for EEG-based MSEs

➢ Our visually scored MSEs could be successfully detected by machine learning algorithms

➢ Automatically scored MSEs correlated to driving performance
CONCLUSION

- Developed the first visual scoring criteria for EEG-based MSEs
- Our visually scored MSEs could be successfully detected by machine learning algorithms
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CONCLUSION

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- Our visually scored MSEs could be successfully detected by machine learning algorithms
- Automatically scored MSEs correlated to driving performance
CONCLUSION

EEG-based MSEs provide a tool to improve the objective assessment of the borderland between wakefulness and sleep.
FUNDING AND ACKNOWLEDGEMENTS
FUNDING

- Swiss National Science Foundation (SNSF, grants 32003B_146643 and 32003B_176323)
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Prof. Dr. P. Achermann

Dr. J. Skorucak

University of Zurich

Dr. A. Malafeev
THANKS FOR STAYING AWAKE!

Apéro in Room 148B (Aufenthaltsraum - SWEZ)