Fast spindle clustering declines with age and shows opposite associations with memory consolidation and NREM sleep fragmentation

Pierre Champetier[1,2], Claire André[1,2], Stéphane Rehel[1,2], Frederik D. Weber[3], Valentin Ourry[1,2], Vincent de la Sayette[1,4], Géraldine Poisnel[1], Antoine Lutz[5], Denis Vivien[1], Gaël Chételat[1], Géraldine Rauchs[1] & the Medit-Ageing Research Group

1 Normandie Univ, UNICAEN, INSERM, U1237, PhIND, Institut Blood and Brain @ Caen-Normandie, GIP Cyceron, Caen, France.
2 Normandie Univ, UNICAEN, PSL Université, EPHE, INSERM, U1077, CHU de Caen, GIP Cyceron, NIMH, Caen, France.
3 Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, 72076 Tübingen, Germany.
4 Neurology department, Caen University Hospital, Caen, France.
5 Lyon Neuroscience Research Center INSERM U1028, CNRS UMR5292, Lyon 1 University, Lyon, France.

AgeWell

Introduction

Several fast spindle parameters (density, amplitude, duration) are impaired with age [1]. Recent studies in rodents and in young adults have shown that fast spindle band power fluctuates at a 0.02-Hz infraslow scale during NREM sleep [2,3]. These fluctuations result from a periodic clustering of spindles and are thought to modulate sleep maintenance and the efficiency of memory consolidation [2,4,5]. However, these dynamic aspects of NREM sleep have not been investigated so far in older adults.

Aims

1) To compare fast spindle band power fluctuations in young and older adults.
2) To better characterize fast spindle clustering (impact of age, effects on spindle features, links with memory consolidation and sleep fragmentation).

Participants & Methods

✓ Participants

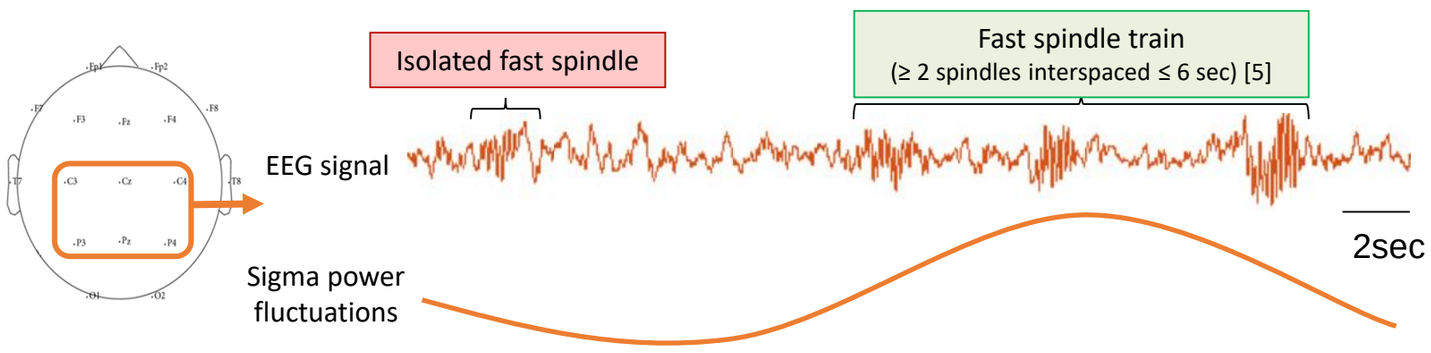
147 older adults (134 from the Age-Well RCT [6]) and 32 young-middle aged adults (Table 1).

✓ At-home polysomnography (PSG)

NREM sleep measures (after artefact rejection):

-***Fast spindle*** (density, amplitude, duration, frequency, clustering in trains, power fluctuations) using individual frequency band centered on fast spindle power peak (mean ± SD: 13.66 ± 0.5 Hz).

-***NREM sleep fragmentation*** (number of micro-arousals during NREM sleep / NREM sleep minute).



✓ Statistical analyses

-Linear mixed models :

spindle clustering level ~ % of fast spindle in trains * age group (covariate: sex)

spindle clustering level ~ spindle characteristics (covariates: age, sex)

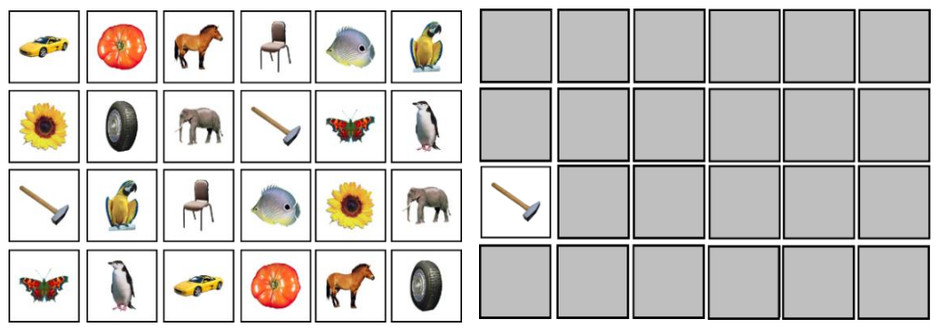
-Linear regressions :

fast spindle train length ~ overnight change (OC) in memory performance and NREM sleep fragmentation (covariates: age, sex)

✓ Memory consolidation assessment

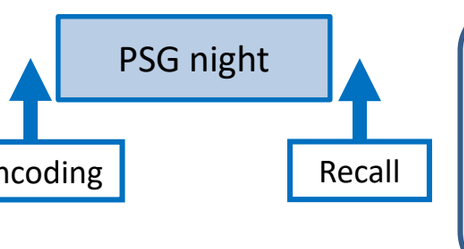
Adapted from Rasch et al. [7]

n = 57 older adults



Learning criterion: 67% of correct answers.

Where is the other hammer?



Overnight change (OC) in memory performance = $100 \times \frac{recall - encoding}{encoding}$

Results

Variable (mean ± SD)	Young-middle aged adults (n=32)	Older adults (n=147)	
Age (year)	34.5 ± 10.9	69.3 ± 4.1	***
Sex ratio (M/F)	22/10	58/89	**
Total sleep time (min)	419.6 ± 56.2	360.5 ± 63.7	***
% N1	10.6 ± 4.4	14.0 ± 7.5	***
% N2	45.8 ± 8.9	47.6 ± 9.1	
% N3	23.4 ± 7.8	20.3 ± 9.8	*
% REM	20.2 ± 5.6	18.0 ± 5.8	*
NREM sleep fragmentation (number of micro-arousals/h)	10.5 ± 6.1	27.6 ± 13.8	***
Fast spindle density	5.3 ± 0.6	4.1 ± 0.7	***
% fast spindle in trains	75.2 ± 4.1	67.5 ± 5.9	***
OC in memory performance† (%)	NA	-26.3 ± 20.7	

† : n=57

Table 1. Participant characteristics.

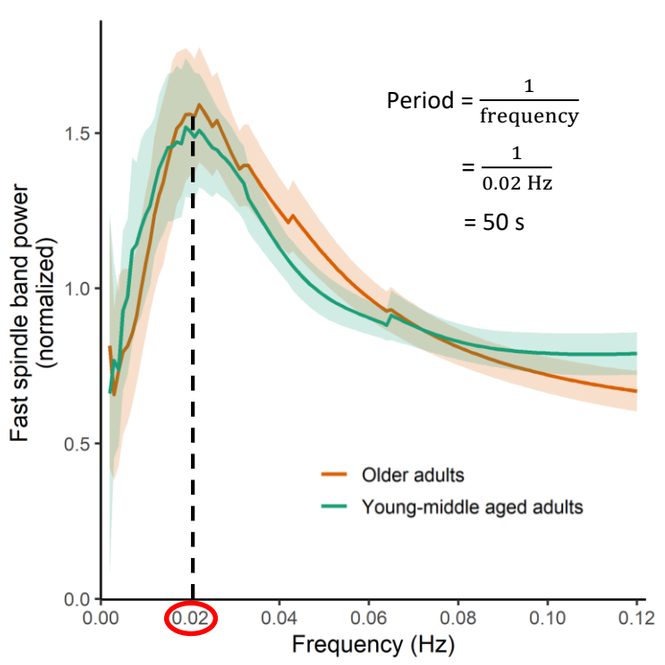


Fig 1. Fast Fourier Transform of fast spindle power time course during NREM sleep peaks at ~0.02 Hz.

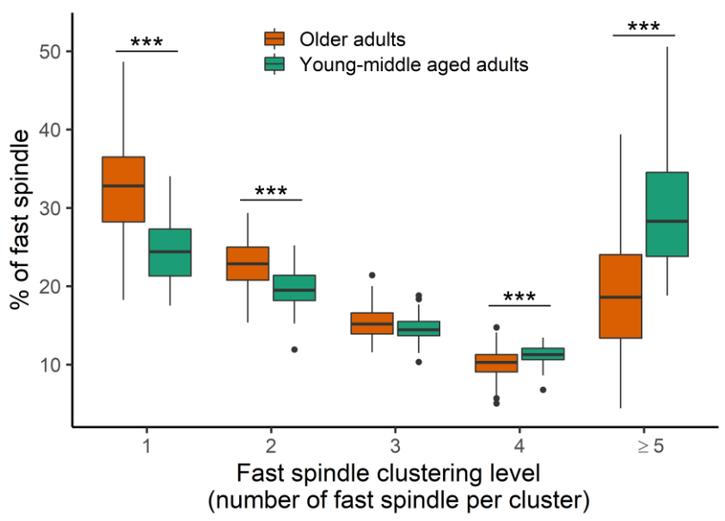


Fig 2. Fast spindle clustering is reduced in ageing.

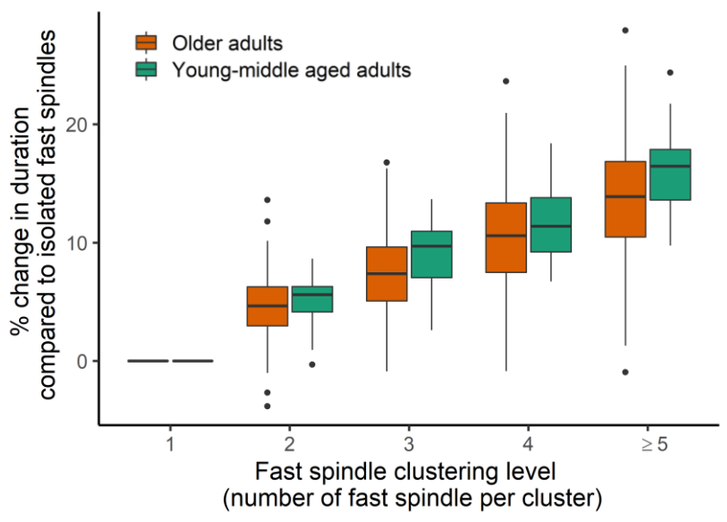


Fig 3. Fast spindle duration increases with fast spindle clustering.

Mean fast spindle train length (number of spindle per train) was :

→ **Negatively** associated with NREM sleep fragmentation (β = - 0.16, p = 0.033)

→ **Positively** associated with OC in memory performance (β = 0.29, p = 0.036)

** : p < 0.05*
*** : p < 0.01*
**** : p < 0.001*

Discussion & Conclusion

- ✓ We found the first evidence that **fast spindle power fluctuates in older adults** with the same ~50s periodicity as in young adults (Fig. 1).
- ✓ However, **fast spindle clustering is reduced in ageing** (Fig. 2). Compared to young-middle aged participants, older adults had more isolated or short trains of 2 fast spindles but fewer longer trains of 4 or more spindles.
- ✓ Moreover, **the clustering of fast spindles modulated their characteristics**, such that fast spindles in long trains exhibited increased duration (Fig. 3), and amplitude (not shown) compared to isolated fast spindles.
- ✓ Finally, the **mean number of fast spindles per train** was negatively associated with NREM sleep fragmentation and positively associated with memory consolidation.

➔ This new way of studying sleep spindles appears to be particularly promising and relevant in the context of memory and ageing.

References

[1] Fernandez & Lüthi, *Physiol Rev.* (2020)
[2] Lecci et al., *Science Advances* (2017)
[3] Weber et al., *NeuroImage* (2021)
[4] Solano et al., *Front Neurosci.* (2022)
[5] Boutin & Doyon, *Philos Trans R Soc Lond B Biol Sci.* (2020)
[6] Poisnel et al., *Alzheimer's and Dementia: Transl Res Clin Interv.* (2018)
[7] Rasch et al., *Science.* (2007)

Acknowledgements

The Age-Well randomized clinical trial is part of the Medit-Ageing project supported by the European Union's Horizon 2020 Research and Innovation Program (grant agreement N° 667696), Institut National de la Santé et de la Recherche Médicale, Région Normandie, and Fondation d'Entreprise MMA des Entrepreneurs du Futur.
We acknowledge the members of the Medit-Ageing Research Group, Minerva and Euclid's teams, the sponsor (Pôle de Recherche Clinique at Inserm), and all the participants of the trial.

Websites: https://silversantestudy.eu/ and http://www.chetelat-lab.fr/

Contact

champetier@cyceron.fr
@Champetier_P