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Navigating the waves of cluster headache: clinical aspects and GON modulation

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PORTFOLIO CHAPTER

Narrative overview of the PhD trajectory

In 2015, during the second year of my medical studies, I met Rolf, which initiated my early PhD involvement. After an initial scientific internship on circadian rhythmicity in metabolomics, I became interested in combining circadian biology with neurology. This led to my introduction to cluster headache research. I entered the Honours MD/PhD track and collaborated with Rolf and Johanna Meijer (Professor of Biological Rhythms) on a narrative review entitled “*The Biological Clock in Cluster Headache*” (incorporated in the thesis **introduction**). In parallel, I collaborated with Ilse de Coo on a study of illicit drug use in cluster headache. I arranged the control dataset, performed the analyses, and drafted the resulting manuscript (**Chapter 3**) and presented results at the International Headache Conference 2017 in Vancouver.

In 2022, I commenced my full-time PhD on cluster headache, after graduating and gaining clinical experience as a hospital physician. I collaborated with Roemer Brandt on a case series of transient side-shifts after GON infiltrations (**Chapter 8**), which I presented as a poster at the European Headache Conference (EHC). During the first year, I took the lead in ethical approval applications for multiple studies (e.g., the *REGON trial NL-OMON56462* and the studies reported in **Chapters 4 and 5**). I initiated and coordinated two multicenter randomized controlled trials: the investigator-initiated *REGON trial*, studying repeated GON injections in chronic cluster headache, and the commercial *RESOLUTION trial*, testing intravenous eptinezumab combined with behavioral intervention in patients with chronic migraine and medication overuse. For the *REGON trial*, I was responsible for trial set-up, progress, and administration until the end of my PhD. For the *RESOLUTION trial*, I managed the Dutch study site, contributed to financial negotiations and logistics, and oversaw recruitment. Together with a student team that I recruited, organized, and supervised over two years, we exceeded the inclusion target of 40 participants.

Throughout my PhD, I supervised more than ten medical students during internships on cluster headache projects. I also contributed annually to teaching activities in courses such as *Hersenen tot Aansturing*, *Half Minor Translation Neuroscience*, and *Clinical Brain and Cognition*. Additionally, I treated patients with cluster headache weekly in our outpatient headache clinic. To support my methodological training, I completed courses on responsible research (BROK), biostatistics, and advanced survival analysis in the first year. Later, I followed additional courses on regression analysis and repeated measurements, and I learned to use R for statistical analyses.

In 2023, I completed the translation and validation of the Cluster Headache Ques-

tionnaire (CHQ) into Dutch (**Chapter 6**), which has since been implemented in ongoing and future studies. That year, I also contributed to a study on risk-reward seeking behavior in cluster headache patients (**Chapter 4**), a follow-up to the illicit drug use study (**Chapter 3**). I presented these findings at the International Headache Conference (IHC) and the EHC 2023, and I participated in the IHEAD meeting in Seoul, which expanded my international collaborations.

In 2024, I worked on the BLINK project (**Chapter 9**), developing a method for R2 latency determination, performing advanced statistical analyses and presenting the results at the EHC. I also conceptualized and executed a study on the natural course and remission of cluster headache, leading to a publication (**Chapter 2**) and presentations at the EHC 2024 (poster) and the European Academy of Neurology (EAN) 2025 (oral). Over the course of 2024, I established a new patient database to improve recruitment and communication for cluster headache research. This initiative included developing a visual identity, a social media presence, and a website to connect with patients and disseminate research results.

In 2025, building on the implemented Dutch CHQ, I designed and conducted a study on its ability to measure quality of life changes, re-using data from ongoing trials (**Chapter 7**). This project was published in 2025 and presented at the EHC. The hormone study in male cluster headache patients, initiated in 2022, was also completed in 2025. The analyses were included in **Chapter 5** and, together with the CHQ results (**Chapter 7**), were presented as posters at the EHC 2025. For the REGON trial, I developed a Statistical Analysis Plan and prepared R scripts in anticipation of unblinding. To finalize my thesis, I wrote the Introduction and Discussion chapters of my thesis and I was responsible for the final formatting, including the cover design. This marked the conclusion of my PhD trajectory, integrating all research activities, analyses, and publications conducted throughout my doctoral studies.



Table 1. Publication and Dissemination Table

Naber WC, Fronczek R, Haan J, Doesborg P, Colwell CS, Ferrari MD, Meijer JH. The biological clock in cluster headache: A review and hypothesis. Cephalalgia. 2019		
Chapter in this thesis	Number 1 (incorporated in introduction)	
Publication in peer reviewed journal	https://journals.sagepub.com/doi/10.1177/0333102419851815 DOI: 10.1177/0333102419851815	
de Coe IF, Naber WC, Wilbrink LA, Haan J, Ferrari MD, Fronczek R. Increased use of illicit drugs in a Dutch cluster headache population. Cephalalgia. 2019		
Chapter in this thesis	3	
Conference contribution of the PhD Candidate	Poster presentation, International Headache Conference 2017 Vancouver	
Publication in peer reviewed journal	https://journals.sagepub.com/doi/10.1177/0333102418804160/ DOI: 10.1177/0333102418804160	
Brandt RB, Naber WC, Ouwehand RH, Haan J, Ferrari MD, Fronczek R. Transient side shift of cluster headache attacks after unilateral greater occipital nerve injection. Headache. 2023		
Chapter in this thesis	8	
Conference contribution of the PhD Candidate	Poster presentation, European Headache Conference Vienna 2022	
Publication in peer reviewed journal	https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.14587 DOI: 10.1111/head.14587	
Naber WC, Brandt RB, Figetakis DD, Jahanshahi M, Terwindt GM, Fronczek R. Translating the Cluster Headache Quality of Life Questionnaire (CHQ) from English to Dutch with the TRAPD method. Neurological Sciences. 2024		
Chapter in this thesis	6	
Publication in peer reviewed journal	https://link.springer.com/article/10.1007/s10072-023-07088-x DOI: 10.1007/s10072-023-07088-x	
Naber WC, van Tilborg PJ, Tannemaat MR, Niesters M, Hellinga MD, Brandt RB, Fronczek R. Beneficial effect of infiltration around the greater occipital nerve in cluster headache independent of modulation of the nociceptive blink reflex. Headache. 2025		
Chapter in this thesis	9	
Conference contribution of the PhD Candidate	Poster presentation, European Headache Conference Rotterdam 2024	

Table 1. Continued

Publication in peer reviewed journal	https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.14946 DOI: 10.1111/head.14946	
Naber W, van Tilborg P, Zuidgeest A, Wilbrink L, Mulleners W, Brandt R, Fronczek R. Exploration of Prolonged Remission and the Natural Course of Cluster Headache: An Interview-Based Cohort Study. Neurology. 2025		
Chapter in this thesis	2	
Conference contribution of the PhD Candidate		Poster presentation, European Headache Conference Rotterdam 2024
Publication in peer reviewed journal		Oral presentation, European Academy of Neurology Conference 2025 https://www.neurology.org/doi/10.1212/WNL.000000000000213795 DOI: 10.1212/WNL.000000000000213795
Naber WC, van Tilborg PJ, Brandt RB, Jansen JJ, Wilbrink P, Kurt E, Leen W, Huygen F, Bijlenga D, Fronczek R Quality of life changes in cluster headache: convergent validity, responsiveness and interpretability. Headache 2025.		
Chapter in this thesis	7	
Conference contribution of the PhD Candidate		Poster presentation, European Headache Conference Lisbon 2025
Publication in peer reviewed journal		https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.15083 doi: 10.1111/head.15083
Naber WC, Brandt RB, Morales- Grooters, M, van den Wal, R, van den Berg SAA, Goemand JJ, Maassen van den Brink A, Fronczek R. Biochemical profiling and symptomatology of androgen deficiency in Males with Cluster Headache – A prospective Case-Controlled study.		
Chapter in this thesis	5	
Conference contribution of the PhD Candidate		Poster presentation, European Headache Conference Lisbon 2025
Publication in peer reviewed journal		Submitted
Brandt RB, Naber WC, Ghobrial J, Boeije R, Mehrabi H, De Leeuw M, Ferrari MD, Fronczek R. Risk and reward seeking behaviour in episodic cluster headache - A psychometric and behavioural study.		
Chapter in this thesis	4	
Conference contribution of the PhD Candidate		Poster presentation, European Headache Conference Barcelona 2023
Publication in peer reviewed journal		Poster presentation, International Headache Conference 2023 Seoul https://link.springer.com/article/10.1007/s10072-025-08663-0 doi: 10.1007/s10072-025-08663-0



Table 2. Tabular overview of completed courses and other training

Completed courses and other training		
Mandatory activities		
<i>Month/year</i>	<i>Title</i>	<i>EC/hours</i>
01 / 2022	Workshop Scientific Conduct for PhDs	5
01 / 2022	Responsible Research (BROK)	42
02 / 2022	Basic Methods and Reasoning in Biostatistics	42
03 / 2022	Leiden University Onboarding Programme Inform & Connect	10
Scientific Course, Workshops and other training activities		
06 / 2022	Survival Analysis Statistical Course	42
06 / 2022	Leiden Headache Center into a new era	10
12 / 2022	European Headache Conference 2022	40
04 / 2023	Statistical aspects of Clinical Trials 2023	28
03 / 2023	PhD course: Regression Analysis	42
06 / 2023	Analysis of Repeated Measurements 2023	42
09 / 2023	IHEAD 2023 - Seoul	18
09 / 2023	International Headache Conference 2023	40
12 / 2023	European Headache Conference 2023	40
12 / 2024	European Headache Conference 2024	40
06 / 2025	European Academy of Neurology Congress 2025	40
12 / 2025	European Headache Conference 2025	40
Transferable skills courses, workshops and other training activities		
05 / 2025	Presenting Skills for Researchers	24
Other Scientific activities related to this thesis		
<i>Month/year</i>	<i>Description</i>	<i>Linked to chapter(s)</i>
09 / 2017	Poster presentation, International Headache Conference 2017	3
12 / 2022	Poster presentation, European Headache Conference 2022	8
09 / 2023	Poster presentation, International Headache Conference 2023	4
12 / 2023	Poster presentation, European Headache Conference 2023	4
12 / 2024	Poster presentation, European Headache Conference 2024	2, 9
06 / 2025	Oral presentation, European Academy of Neurology Congress 2025	2
06 / 2025	Presentation award at Scientific Meeting Neurology LUMC	2
12 / 2025	Poster presentation, European Headache Conference 2025	5, 7



*PhD project chapters are the direct result of the PhD project of the PhD candidate.

Some theses also include Collaboration Chapters, to which the PhD candidate has contributed but fall outside the PhD project.

Figure 1. CRedit statement for the Chapters in this thesis.

Tabular overview of the contribution of the PhD candidate to each chapter in this thesis, according to the CRedit taxonomy. The color range from light orange to red represents the level of contribution to the task: the redder, the higher the contribution.

CURRICULUM VITAE

Willemijn Naber was born on July 26th, 1994 in Tilburg, the Netherlands, where she also grew up. She attended secondary school at Odulphus lyceum in Tilburg (2007-2013). In 2013 she moved to Leiden to study Medicine at Leiden University. For her bachelor's electives, she completed the minor Translational Neuroscience. During her bachelor's programme, she followed the MD/PhD Excellence student track of the Honours College. Through this track she first met Dr. Fronczek and started on an extracurricular internship in cluster headache research, which continued throughout her studies under supervision of Prof. dr. M.D Ferrari and Prof. dr. J.H. Meijer. In 2017, she attended the International Headache Conference, where she presented her first manuscript as poster on illicit drug use in cluster headache. She also completed a review on the biological clock in cluster headache.

She dedicated her final year of her master's programme to neurology, completing a research internship on myasthenia gravis and elective internships in neurology and neuroradiology. After graduation, she gained clinical experience as resident at the Neurology department of the Haga Hospital in The Hague. In 2021, she resumed research through a full PhD track at the Department of Neurology at Leiden University Medical Center under supervision of Prof. dr. G.M. Terwindt, Dr. R Fronczek and Dr. W.M. Mulleners. The results of this work are described in this thesis. During her PhD she presented her work on multiple international conferences.. She also supervised several master's students during their research projects and was actively involved in teaching medical students in the field of neurology. In addition, she combined her research with clinical work at the headache outpatient clinic.

After completion of her thesis, she worked as a resident at the Neurology department at the St. Antonius hospital in Nieuwegein. She is currently working as a resident at the Department of Neurology at Leiden University Medical Center. Willemijn lives in Utrecht with her partner Dennis.

LIST OF PUBLICATIONS

Naber WC, Brandt RB, Leon Morales - Grooters M, Van der Wal R, Van den Berg SA, Goeman JJ, Maassen Van Den Brink A, Fronczek R. Biochemical profiling and symptomatology of androgen deficiency in men with Cluster Headache – A prospective Case-Controlled study. Submitted.

Naber WC, Brandt RB, Ghobrial J, Boeije R, Mehrabie H, De Leeuw M, Ferrari MD, Fronczek R. Risk and reward seeking behaviour in episodic cluster headache - A psychometric and behavioural study. *Neurol Sci.* 2026 Jan 2;47(1):64

Naber WC, Van Tilborg PT, Brandt RB, Jansen JJ, Wilbrink LB, Kurt E, Leen W, Huygen F, Bijlenga D, Fronczek R. Quality of life changes in cluster headache: convergent validity, responsiveness and interpretability of the Cluster Headache Quality of Life scale (CHQ) as Patient Reported Outcome Measure (PROM). *Headache*. 2026 Jan;66(1):213-229.

Naber WC, Fronczek R. Through the eyes of Janus: Remission and disease activity in cluster headache. *Cephalgia*. 2025 Sep;45(9):3331024251368258.

Naber WC van Tilborg PJ, Zuidgeest A, Wilbrink L, Mulleners WM, Brandt RB, Fronczek R. Exploration of Prolonged Remission and the Natural Course of Cluster Headache: An Interview-Based Cohort Study. *Neurology*. 2025 Jul;105(1):e213795.

Naber WC, van Tilborg PJ, Tannemaat MR, Niesters M, Hellinga MD, Brandt RB, Fronczek R. Beneficial effect of infiltration around the greater occipital nerve in cluster headache independent of modulation of the nociceptive blink reflex. *Headache*. 2025 Apr 24.

Naber WC, Brandt RB, Figetakis DD, Jahanshahi M, Terwindt GM, Fronczek R. Translating the Cluster Headache Quality of Life Questionnaire (CHQ) from English to Dutch with the TRAPD method. *Neurological Sciences*. 2024 Mar;45(3):1217-1224.

Brandt RB*, **Naber WC***, Ouwehand RH, Haan J, Ferrari MD, Fronczek R. Transient side shift of cluster headache attacks after unilateral greater occipital nerve injection. *Headache*. 2023 Sep;63(8):1193-1197

Ruiter AM, Wang Z, Yin Z, **Naber WC**, Simons J, Blom JT, van Gemert JC, Verschuuren JJGM, Tannemaat MR. Assessing facial weakness in myasthenia gravis with facial recognition software and deep learning. *Annals of Clinical and Translational Neurology* 2023 Aug;10(8):1314-1325.

Ruiter AM, **Naber WC**, Verschuuren JJGM, Tannemaat MR. The face of myasthenia gravis. *Neurology* 2020 Jul 14;95(2):89-90

Naber WC, Fronczek R, Haan J, Doesborg P, Colwell CS, Ferrari MD, Meijer JH. The biological clock in cluster headache: A review and hypothesis. *Cephalgia*. 2019 Dec;39(14):1855-1866

de Coö IF*, **Naber WC***, Wilbrink LA, Haan J, Ferrari MD, Fronczek R. Increased use of illicit drugs in a Dutch cluster headache population. *Cephalgia*. 2019 Apr;39(5):626-



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