



Universiteit
Leiden

The Netherlands

The autoimmune hypothesis of narcolepsy and its unexplored clinical features

Schinkelshoek, M.S.

Citation

Schinkelshoek, M. S. (2021, November 11). *The autoimmune hypothesis of narcolepsy and its unexplored clinical features*. Retrieved from <https://hdl.handle.net/1887/3239235>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3239235>

Note: To cite this publication please use the final published version (if applicable).

List of publications

Schinkelshoek MS, Smolders IM, Donjacour CE, van der Meijden WP, van Zwet EW, Fronczek R, Lammers GJ. Decreased body mass index during treatment with sodium oxybate in narcolepsy type 1. *J Sleep Res.* 2019 Jun;28(3):e12684. doi: 10.1111/jsr.12684. Epub 2018 Mar 4.

Schinkelshoek MS, Fronczek R, Kooy-Winkelaar EMC, Petersen J, Reid HH, van der Heide A, Drijfhout JW, Rossjohn J, Lammers GJ, Koning F. H1N1 HA-specific T cells can be readily detected in narcolepsy type 1. *J Neuroimmunol.* 2019 Jul 15;332:167-175. doi: 10.1016/j.jneuroim.2019.04.009. Epub 2019 Apr 17.

Schinkelshoek MS, Lammers GJ, Fronczek R. The development of hypocretin deficiency in narcolepsy type 1 can be swift and closely linked to disease onset: clues from a singular case. *Sleep.* 2019 Apr 1;42(4):zsz009. doi: 10.1093/sleep/zsz009.

Schinkelshoek MS, de Wit K, Bruggink V, Fronczek R, Lammers GJ. Daytime sleep and dream (mis)perception in a Dutch tertiary sleep center population. *Sleep Med.* 2020 May;69:78-84. doi: 10.1016/j.sleep.2019.12.026. Epub 2020 Jan 10.

Schinkelshoek M, Fronczek R, Verduijn W, Haasnoot G, Overeem S, Donjacour C, van der Heide A, Roelen D, Claas F, Lammers GJ. HLA associations in narcolepsy type 1 persist after the 2009 H1N1 pandemic. *J Neuroimmunol.* 2020 Mar 4;342:577210. doi: 10.1016/j.jneuroim.2020.577210. Online ahead of print.

Nascholingsartikel in *Nervus* magazine, maart 2019: 'Oorzaken en behandeling van hypersomnolentie.' Met Jari Gool, dr. Rolf Fronczek en prof. dr. Gert Jan Lammers.

Schinkelshoek MS, Fronczek R, Lammers GJ. Update on the Treatment of Idiopathic Hypersomnia. *Curr Sleep Medicine Rep* 2019;5:207–214. <https://doi.org/10.1007/s40675-019-00158-7>

Schinkelshoek MS, van Luxemburg RP, Bes AL, Ottens TH, Fronczek R, Lammers GJ, van Westerloo DJ. Good night and good luck: sleep in the ICU. *Neth J Crit Care*. 2020 Jan;28(1): 13-17.

Straat ME, *Schinkelshoek MS*, Fronczek R, Lammers GJ, Rensen PCN, Boon MR. Role of Brown Adipose Tissue in Adiposity Associated With Narcolepsy Type 1. *Front Endocrinol (Lausanne)*. 2020 Apr 16;11:145. doi: 10.3389/fendo.2020.00145. eCollection 2020.

Lindström M, *Schinkelshoek MS*, Tienarid PJ, Kukkonen JP, Renkonen R, Fronczek R, Lammers GJ, Itkonen O. Orexin-A measurement in narcolepsy: a stability study and a comparison of LC-MS/MS and immunoassays. *Clin Biochem*. 2021 Feb 1:S0009-9120(21)00025-4. doi: 10.1016/j.clinbiochem.2021.01.009. Epub 2021 Feb 1.

Fronczek R, *Schinkelshoek M*, Shan L, Lammers GJ. The orexin/hypocretin system in neuropsychiatric disorders: Relation to signs and symptoms. *Handb Clin Neurol*. 2021;180:343-358. doi: 10.1016/B978-0-12-820107-7.00021-5. PMID: 34225940.

Dietmann A, Horn MP, *Schinkelshoek MS*, Fronczek R, Salmen A, Bargiotas P, Lammers GJ, Khatami R, Bassetti CLA. Conventional autoantibodies against brain antigens are not routinely detectable in serum and CSF of narcolepsy type 1 and 2 patients. *Sleep Med*. 2020 Aug 7;75:188-191. doi: 10.1016/j.sleep.2020.08.001. Online ahead of print.

Talebian Yazdi M, Egberts J, *Schinkelshoek MS*, Wolterbeek R, Nabers J, Venmans BJ, Tournoy KG, Annema JT. Endosonography for lung cancer staging: predictors for false-negative outcomes. *Lung Cancer*. 2015 Dec;90(3):451-6. doi: 10.1016/j.lungcan.2015.09.020. Epub 2015 Sep 25. PMID: 26477967.

Talebian Yazdi M, *Schinkelshoek MS*, Loof NM, Taube C, Hiemstra PS, Welters MJ, van der Burg SH. Standard radiotherapy but not chemotherapy impairs systemic immunity in non-small cell lung cancer. *Oncoimmunology*. 2016 Nov 8;5(12):e1255393. doi: 10.1080/2162402X.2016.1255393. PMID: 28123900; PMCID: PMC5214754.

Tresoldi AS, Sburlati LF, Rodari M, *Schinkelshoek MS*, Perrino M, De Leo S, Montefusco L, Colombo P, Arosio M, Lania AGA, Fugazzola L, Chiti A. Radioiodine ablation with 1,850 MBq in association with rhTSH in patients with differentiated thyroid cancer. *J Endocrinol Invest*. 2014 Aug;37(8):709-714. doi: 10.1007/s40618-014-0088-3. Epub 2014 May 21. Erratum in: *J Endocrinol Invest*. 2018 Apr 2;: PMID: 24844565.

Schinkelshoek MS, Lopci E, Clerici E, Alongi F, Mancosu P, Rodari M, Navarra P, van der Hiel B, Scorsetti M, Chiti A. Impact of 11C-methionine positron emission tomography/computed tomography on radiation therapy planning and prognosis in patients with primary brain tumors. *Tumori*. 2014 Nov-Dec;100(6):636-44. doi: 10.1700/1778.19268. Erratum in: *Tumori*. 2018 Dec;104(6):480. PMID: 25688497.

Lopci E, *Schinkelshoek MS*, Alongi F, Antunovic L, Arcangeli S, Ascolese A, Bettinardi V, Lobefalo F, Mancosu P, Pepe G, Reggiori G, Rodari M, Rossi P, Tosi H, Tozzi S, Scorsetti M, Chiti A (2014). Chapter 29: PET/CT hybrid imaging in radiotherapy planning. In Aktolun C, Goldsmith SJ (eds.). *Nuclear Oncology* (pp. 432-56). Philadelphia, Pennsylvania, USA: Wolters Kluwer Health.

Dankwoord

In dit dankwoord richt ik me ten eerste tot de mensen met narcolepsie en alle andere deelnemers die hun energie en tijd hebben gegeven om de in dit proefschrift uitgeschreven onderzoeken mogelijk te maken. Ik realiseer me terdege dat deelname aan wetenschappelijk onderzoek niet vanzelfsprekend is. Pauline, het is heel fijn om tijdens je werk aan een half woord genoeg te hebben om te begrijpen wat de ander bedoelt. Dank dat ik zo met je mocht werken.

Yvonne, ik heb genoten van je verhalen en me gelaafd aan je ervaring; met dezelfde geestdrift stort je je nu op nieuwe avonturen tijdens je pensioen. Paul, Judith en alle andere KNF-laboranten, Stephan, en alle studenten: dank voor jullie onmisbare hulp tijdens mijn promotietijd.

Gert en Martijn, dank dat ik als slaapverstekeling mijn plek mocht hebben in jullie domein, het heeft mijn tijd als promovendus verrijkt.

Mede-slaappromovendi, Mojca, Adrienne en Jari: ik heb niet alleen mooie congressen met jullie meegemaakt, maar ook veel van en met jullie geleerd. Uitdagingen zijn vaak te overwinnen door met elkaar mee te denken.

Ulf, Claudio en alle andere BeLeWi-onderzoekers: de internationale samenwerking, maar ook de persoonlijke band die wij in de afgelopen jaren hebben opgebouwd, vervult mij met trots.

Dan het team bij SEIN: een hechte groep mensen met eenzelfde doel voor ogen. Vooruitstrevend zijn met de patiënt in het middelpunt, is wat elk behandelteam zou moeten nastreven.

Frits, mijn promotor vanuit immunologische hoek, dank voor je nuchtere begeleiding, het kritisch meedenken en de mogelijkheden die je hebt geschapen om de onderzoeken uiteengezet in dit proefschrift uit te kunnen voeren.

Rolf en Gert Jan, ik denk niet dat ik me betere begeleiders in dit traject had kunnen wensen. Jullie hebben me geïnspireerd en de kansen geboden mezelf op alle vlakken te ontwikkelen tot een betere en meer volwassen onderzoeker, dokter en, naar ik hoop, mens.

Mijn ouders, Ria en Johan en Sarah en Job, de steun die ik van jullie ontvang, zorgt ervoor dat ik op koers ben gebleven naar dit eindpunt. Jullie zijn onmisbaar en staan dichterbij mij dan ooit.

Shita, en Ivar, mijn gezin. We hebben de afgelopen jaren veel grote stappen gezet in ons leven, met als absoluut hoogtepunt de geboorte van Ivar. Door jullie kan ik doorzetten als ik geen zin heb, kan ik vrolijk zijn zelfs als het tegen zit en weet ik dat alles goed komt.

Curriculum vitae

Mink Sebastian Schinkelshoek was born in Leiden, the Netherlands, on June 7, 1990 as Ria Bleeker's and Johan Schinkelshoek's first child. Two years later, his brother Job was born. He grew up in Voorhout.

In 2008 he finished secondary school at the Stedelijk Gymnasium Leiden *summa cum laude* and started studying Medicine at Leiden University in the same year. He soon became interested in Neurology and hence started working as a student-assistant at the Department of Anatomy in his second year, where he assisted in neuro-anatomy dissection courses to first-year medical students for 2 years. He acquired his Bachelor's degree in Medicine in 2011 and meanwhile started a Pre-Master Biomedical Sciences that prepared for the Master program of Biomedical Sciences at the same institute to ascertain whether biomedical research was a venue to be further explored. This Pre-Master and the following Master in Biomedical Sciences convinced him that pursuing a career in neurology combining both clinical work and research was his prime ambition. In 2015, he obtained both Medicine and Biomedical Sciences Master's degrees *cum laude*. During the last part of his clinical rotations he got in touch with narcolepsy research.

After graduating, he started working as a Neurology resident not in training in the Reinier de Graaf hospital in Delft. Meanwhile, the plan that eventually led to this thesis was forged in the months that he worked in Delft. In November 2016 the PhD on the autoimmune hypothesis started at the Department of Neurology of the Leiden University Medical Center and the Sleep-Wake Centre of Stichting Epilepsie Instellingen Nederland (SEIN) in Heemstede. In 2018, he was awarded the Young Investigator Award at the 7th International Symposium on Narcolepsy in Beverly, MA, USA for his work on the composition of the immune system in narcolepsy type 1. Additionally, he received several travel grants (EAN 2017 and EAN 2019) and won the Best Poster Award at the 2017 European Narcolepsy Day.

Mink Schinkelshoek and his partner Shita Bakker became parents of Ivar Schinkelshoek on 21 September 2019, they live in Voorhout. He is currently working as a resident in training at the Department of Neurology of the Leiden University Medical Center.

References

- Adams, P. D., Afonine, P. V., Bunkoczi, G., Chen, V. B., Davis, I. W., Echols, N., Headd, J. J., Hung, L. W., Kapral, G. J., Grosse-Kunstleve, R. W., McCoy, A. J., Moriarty, N. W., Oeffner, R., Read, R. J., Richardson, D. C., Richardson, J. S., Terwilliger, T. C. & Zwart, P. H. 2010. PHENIX: a comprehensive Python-based system for macromolecular structure solution. *Acta Crystallogr D Biol Crystallogr*, 66, 213-21.
- Ahmed, S. S., Volkmut, W., Duca, J., Corti, L., Pallaoro, M., Pezzicoli, A., Karle, A., Rigat, F., Rappuoli, R., Narasimhan, V., Julkunen, I., Vuorela, A., Vaarala, O., Nohynek, H., Pasini, F. L., Montomoli, E., Trombetta, C., Adams, C. M., Rothbard, J. & Steinman, L. 2015. Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2. *Sci Transl Med*, 7, 294ra105.
- Ambati, A., Poiret, T., Svahn, B. M., Valentini, D., Khademi, M., Kockum, I., Lima, I., Arnheim-Dahlstrom, L., Lamb, F., Fink, K., Meng, Q., Kumar, A., Rane, L., Olsson, T. & Maeurer, M. 2015. Increased beta-haemolytic group A streptococcal M6 serotype and streptodornase B-specific cellular immune responses in Swedish narcolepsy cases. *J Intern Med*, 278, 264-76.
- American Academy of Sleep Medicine 2014. *International Classification of Sleep Disorders*, Darien, IL, American Academy of Sleep Medicine.
- Aran, A., Lin, L., Nevsimanova, S., Plazzi, G., Hong, S. C., Weiner, K., Zeitzer, J. & Mignot, E. 2009. Elevated anti-streptococcal antibodies in patients with recent narcolepsy onset. *Sleep*, 32, 979-83.
- Aserinsky, E. & Kleitman, N. 1953. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science*, 118, 273-4.
- Attarian, H. P., Duntley, S. & Brown, K. M. 2004. Reverse sleep state misperception. *Sleep Med*, 5, 269-72.
- Bassetti, C. L. A., Adamantidis, A., Burdakov, D., Han, F., Gay, S., Kallweit, U., Khatami, R., Koning, F., Kornum, B. R., Lammers, G. J., Liblau, R. S., Luppi, P. H., Mayer, G., Pollmacher, T., Sakurai, T., Sallusto, F., Scammell, T. E., Tafti, M. & Dauvilliers, Y. 2019. Narcolepsy - clinical spectrum, aetiopathophysiology, diagnosis and treatment. *Nat Rev Neurol*.
- Bastien, C. H., Ceklic, T., St-Hilaire, P., Desmarais, F., Perusse, A. D., Lefrancois, J. & Pedneault-Drolet, M. 2014. Insomnia and sleep misperception. *Pathol Biol (Paris)*, 62, 241-51.
- Bianchi, M. T., Wang, W. & Klerman, E. B. 2012. Sleep misperception in healthy adults: implications for insomnia diagnosis. *J Clin Sleep Med*, 8, 547-54.
- Bishop, C., Rosenthal, L., Folkerts, M., Nykamp, K., Helmus, T., Guido, P., Syron, M. L., Roehrs, T., Rice, M. & Roth, T. 1998. The perception of sleep as a function of the level of daytime sleepiness among patients with obstructive sleep apnea. *Compr Psychiatry*, 39, 312-7.
- Black, J. L., 3rd, Silber, M. H., Krahn, L. E., Avula, R. K., Walker, D. L., Pankratz, V. S., Fredrickson, P. A. & Slocumb, N. L. 2005. Studies of humoral immunity to preprohypocretin in human leukocyte antigen DQB1*0602-positive narcoleptic subjects with cataplexy. *Biol Psychiatry*, 58, 504-9.
- Black Sw, Yamanaka a, Kilduff Ts 2015. Challenges in the development of therapeutics for narcolepsy. *Prog Neurobiol*.
- Black, S. W., Yamanaka, A. & Kilduff, T. S. 2017. Challenges in the development of therapeutics for narcolepsy. *Prog Neurobiol*, 152, 89-113.
- Bomfim, I. L., Lamb, F., Fink, K., Szakacs, A., Silveira, A., Franzen, L., Azhary, V., Maeurer, M., Feltelius, N., Darin, N., Hallbook, T., Arnheim-Dahlstrom, L., Kockum, I. & Olsson, T. 2017. The immunogenetics of narcolepsy associated with A(H1N1)pdm09 vaccination (Pandemrix) supports a potent gene-environment interaction. *Genes Immun*, 18, 75-81.
- Bonnet, M. H. & Arand, D. L. 1997. Physiological activation in patients with Sleep State Misperception. *Psychosom Med*, 59, 533-40.
- Boscolo-Berto R, Viel G, Montagnese, Et Al 2012. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. *Sleep Med Rev*, 16, 431-43.
- Brochet, X., Lefranc, M. P. & Giudicelli, V. 2008. IMGT/V-QUEST: the highly customized and integrated system for IG and TR standardized V-J and V-D-J sequence analysis. *Nucleic Acids Res*, 36, W503-8.

- Broughton, S. E., Petersen, J., Theodossis, A., Scally, S. W., Loh, K. L., Thompson, A., Van Bergen, J., Kooy-Winkelaar, Y., Henderson, K. N., Beddoe, T., Tye-Din, J. A., Mannering, S. I., Purcell, A. W., Mccluskey, J., Anderson, R. P., Koning, F., Reid, H. H. & Rossjohn, J. 2012. Biased T cell receptor usage directed against human leukocyte antigen DQ8-restricted gliadin peptides is associated with celiac disease. *Immunity*, 37, 611-21.
- Castillo, J., Goparaju, B. & Bianchi, M. T. 2014. Sleep-wake misperception in sleep apnea patients undergoing diagnostic versus titration polysomnography. *J Psychosom Res*, 76, 361-7.
- Cavallero, C., Cicogna, P., Natale, V., Occhionero, M. & Zito, A. 1992. Slow wave sleep dreaming. *Sleep*, 15, 562-6.
- Chellappa, S. L., Munch, M., Blatter, K., Knoblauch, V. & Cajochen, C. 2009. Does the circadian modulation of dream recall modify with age? *Sleep*, 32, 1201-9.
- Choi, S. J., Suh, S., Ong, J. & Joo, E. Y. 2016. Sleep Misperception in Chronic Insomnia Patients with Obstructive Sleep Apnea Syndrome: Implications for Clinical Assessment. *J Clin Sleep Med*, 12, 1517-1525.
- Cochran, W. G. 1954. Some Methods for Strengthening the Common χ^2 Tests. *Biometrics*, 10, 417-451.
- Cogswell, A. C., Maski, K., Scammell, T. E., Tucker, D., Orban, Z. S. & Koralnik, I. J. 2019. Children with Narcolepsy type 1 have increased T-cell responses to orexins. *Ann Clin Transl Neurol*.
- Cvetkovic-Lopes, V., Bayer, L., Dorsaz, S., Maret, S., Pradervand, S., Dauvilliers, Y., Lecendreux, M., Lammers, G. J., Donjacour, C. E., Du Pasquier, R. A., Pfister, C., Petit, B., Hor, H., Muhlethaler, M. & Tafti, M. 2010. Elevated Tribbles homolog 2-specific antibody levels in narcolepsy patients. *J Clin Invest*, 120, 713-9.
- Dalal, J., Roh, J. H., Maloney, S. E., Akuffo, A., Shah, S., Yuan, H., Wamsley, B., Jones, W. B., De Guzman Strong, C., Gray, P. A., Holtzman, D. M., Heintz, N. & Dougherty, J. D. 2013. Translational profiling of hypocretin neurons identifies candidate molecules for sleep regulation. *Genes Dev*, 27, 565-78.
- Daniels, L. 1934. Narcolepsy. *Medicine*, 13, 1-122.
- Dauvilliers, Y., Arnulf, I., Lecendreux, M., Monaca Charley, C., Franco, P., Drouot, X., D'ortho, M. P., Launois, S., Lignot, S., Bourgin, P., Nogues, B., Rey, M., Bayard, S., Scholz, S., Lavault, S., Tubert-Bitter, P., Saussier, C. & Pariente, A. 2013. Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France. *Brain*, 136, 2486-96.
- De La Herran-Arita, A. K. & Garcia-Garcia, F. 2014. Narcolepsy as an immune-mediated disease. *Sleep Disord*, 2014, 792687.
- De La Herran-Arita, A. K., Kornum, B. R., Mahlios, J., Jiang, W., Lin, L., Hou, T., Macaubas, C., Einen, M., Plazzi, G., Crowe, C., Newell, E. W., Davis, M. M., Mellins, E. D. & Mignot, E. 2013. CD4+ T cell autoimmunity to hypocretin/orexin and cross-reactivity to a 2009 H1N1 influenza A epitope in narcolepsy. *Sci Transl Med*, 5, 216ra176.
- De La Herran-Arita, A. K., Kornum, B. R., Mahlios, J., Jiang, W., Lin, L., Hou, T., Macaubas, C., Einen, M., Plazzi, G., Crowe, C., Newell, E. W., Davis, M. M., Mellins, E. D. & Mignot, E. 2014. Retraction of the research article: "CD4(+) T cell autoimmunity to hypocretin/orexin and cross-reactivity to a 2009 H1N1 influenza A epitope in narcolepsy". *Sci Transl Med*, 6, 247rt1.
- De Lecea, L., Kilduff, T. S., Peyron, C., Gao, X., Foye, P. E., Danielson, P. E., Fukuhara, C., Battenberg, E. L., Gautvik, V. T., Bartlett, F. S., 2nd, Frankel, W. N., Van Den Pol, A. N., Bloom, F. E., Gautvik, K. M. & Sutcliffe, J. G. 1998. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc Natl Acad Sci U S A*, 95, 322-7.
- De Vries, N. L., Van Unen, V., Ijsselstein, M. E., Abdelaal, T., Van Der Breggen, R., Farina Sarasqueta, A., Mahfouz, A., Peeters, K., Holtt, T., Lelieveldt, B. P. F., Koning, F. & De Miranda, N. 2019. High-dimensional cytometric analysis of colorectal cancer reveals novel mediators of antitumour immunity. *Gut*.
- Dittoni, S., Mazza, M., Losurdo, A., Testani, E., Di Giacopo, R., Marano, G., Di Nicola, M., Farina, B., Mariotti, P., Mazza, S. & Della Marca, G. 2013. Psychological functioning measures in patients with primary insomnia and sleep state misperception. *Acta Neurol Scand*, 128, 54-60.
- Drakatos, P., Patel, K., Thakrar, C., Williams, A. J., Kent, B. D. & Leschziner, G. D. 2016. Sleep-stage sequencing of sleep-onset REM periods in MSLT predicts treatment response in patients with narcolepsy. *J Sleep Res*, 25, 203-10.

- Drakatos, P., Suri, A., Higgins, S. E., Ebrahim, I. O., Muza, R. T., Kosky, C. A., Williams, A. J. & Leschziner, G. D. 2013. Sleep stage sequence analysis of sleep onset REM periods in the hypersomnias. *J Neurol Neurosurg Psychiatry*, 84, 223-7.
- Emsley, P., Lohkamp, B., Scott, W. G. & Cowtan, K. 2010. Features and development of Coot. *Acta Crystallogr D Biol Crystallogr*, 66, 486-501.
- Enevoldsen, L. H., Tindborg, M., Hovmand, N. L., Christoffersen, C., Ellingsgaard, H., Suetta, C., Stallknecht, B. M., Jennum, P. J., Kjaer, A. & Gammeltoft, S. 2018. Functional brown adipose tissue and sympathetic activity after cold exposure in humans with type 1 narcolepsy. *Sleep*.
- Evans, P. 2006. Scaling and assessment of data quality. *Acta Crystallogr D Biol Crystallogr*, 62, 72-82.
- Faraco, J., Lin, L., Kornum, B. R., Kenny, E. E., Trynka, G., Einen, M., Rico, T. J., Lichtner, P., Dauvilliers, Y., Arnulf, I., Lecendreux, M., Javidi, S., Geisler, P., Mayer, G., Pizza, F., Poli, F., Plazzi, G., Overeem, S., Lammers, G. J., Kemlink, D., Sonka, K., Nevsimalova, S., Rouleau, G., Desautels, A., Montplaisir, J., Frauscher, B., Ehrmann, L., Hogg, B., Jennum, P., Bourgin, P., Peraïta-Adrados, R., Iranzo, A., Bassetti, C., Chen, W. M., Concannon, P., Thompson, S. D., Damotte, V., Fontaine, B., Breban, M., Gieger, C., Klopp, N., Deloukas, P., Wijmenga, C., Hallmayer, J., Onengut-Gumusc, S., Rich, S. S., Winkelmann, J. & Mignot, E. 2013. ImmunoChip study implicates antigen presentation to T cells in narcolepsy. *PLoS Genet*, 9, e1003270.
- Feige, B., Al-Shajlawi, A., Nissen, C., Voderholzer, U., Hornyak, M., Spiegelhalter, K., Kloepper, C., Perlis, M. & Riemann, D. 2008. Does REM sleep contribute to subjective wake time in primary insomnia? A comparison of polysomnographic and subjective sleep in 100 patients. *J Sleep Res*, 17, 180-90.
- Feltelius, N., Persson, I., Ahlqvist-Rastad, J., Andersson, M., Arnheim-Dahlstrom, L., Bergman, P., Granath, F., Adori, C., Hokfelt, T., Kuhlmann-Berenzon, S., Liljestrom, P., Maeurer, M., Olsson, T., Ortqvist, A., Partinen, M., Salmonson, T. & Zethelius, B. 2015. A coordinated cross-disciplinary research initiative to address an increased incidence of narcolepsy following the 2009-2010 Pandemrix vaccination programme in Sweden. *J Intern Med*, 278, 335-53.
- Fernandez-Mendoza, J., Calhoun, S. L., Bixler, E. O., Karatazaki, M., Liao, D., Vela-Bueno, A., Jose Ramos-Platon, M., Sauder, K. A., Basta, M. & Vgontzas, A. N. 2011. Sleep misperception and chronic insomnia in the general population: role of objective sleep duration and psychological profiles. *Psychosom Med*, 73, 88-97.
- Ferri, R., Pizza, F., Vandì, S., Ilti, M. & Plazzi, G. 2016. Decreased sleep stage transition pattern complexity in narcolepsy type 1. *Clin Neurophysiol*, 127, 2812-2819.
- Fortuyn, H. A., Swinkels, S., Buitelaar, J., Renier, W. O., Furer, J. W., Rijnders, C. A., Hodiamont, P. P. & Overeem, S. 2008. High prevalence of eating disorders in narcolepsy with cataplexy: a case-control study. *Sleep*, 31, 335-41.
- Fosse, R., Stickgold, R. & Hobson, J. A. 2002. Emotional experience during rapid-eye-movement sleep in narcolepsy. *Sleep*, 25, 724-32.
- Fronczek, R., Overeem, S., Reijntjes, R., Lammers, G. J., Van Dijk, J. G. & Pijl, H. 2008. Increased heart rate variability but normal resting metabolic rate in hypocretin/orexin-deficient human narcolepsy. *J Clin Sleep Med*, 4, 248-54.
- Giannoccaro, M. P., Waters, P., Pizza, F., Liguori, R., Plazzi, G. & Vincent, A. 2017. Antibodies Against Hypocretin Receptor 2 Are Rare in Narcolepsy. *Sleep*, 40.
- Goulart, L. I., Pinto, L. R., Jr., Perlis, M. L., Martins, R., Caboclo, L. O., Tufik, S. & Andersen, M. L. 2014. Effects of different sleep deprivation protocols on sleep perception in healthy volunteers. *Sleep Med*, 15, 1219-24.
- Hamann, D., Kostense, S., Wolthers, K. C., Otto, S. A., Baars, P. A., Miedema, F. & Van Lier, R. A. 1999. Evidence that human CD8+CD45RA+CD27- cells are induced by antigen and evolve through extensive rounds of division. *Int Immunol*, 11, 1027-33.
- Han, F., Faraco, J., Dong, X. S., Ollila, H. M., Lin, L., Li, J., An, P., Wang, S., Jiang, K. W., Gao, Z. C., Zhao, L., Yan, H., Liu, Y. N., Li, Q. H., Zhang, X. Z., Hu, Y., Wang, J. Y., Lu, Y. H., Lu, C. J., Zhou, W., Hallmayer, J., Huang, Y. S., Strohl, K. P., Pollmacher, T. & Mignot, E. 2013. Genome wide analysis of narcolepsy in China implicates novel immune loci and reveals changes in association prior to versus after the 2009 H1N1 influenza pandemic. *PLoS Genet*, 9, e1003880.

- Han, F., Lin, L., Warby, S. C., Faraco, J., Li, J., Dong, S. X., An, P., Zhao, L., Wang, L. H., Li, Q. Y., Yan, H., Gao, Z. C., Yuan, Y., Strohl, K. P. & Mignot, E. 2011. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. *Ann Neurol*, 70, 410-7.
- Hartmann, F. J., Bernard-Valnet, R., Queriaux, C., Mrdjen, D., Weber, L. M., Galli, E., Krieg, C., Robinson, M. D., Nguyen, X. H., Dauvilliers, Y., Liblau, R. S. & Becher, B. 2016. High-dimensional single-cell analysis reveals the immune signature of narcolepsy. *J Exp Med*, 213, 2621-2633.
- Harvey, A. G. & Tang, N. K. 2012. (Mis)perception of sleep in insomnia: a puzzle and a resolution. *Psychol Bull*, 138, 77-101.
- Henderson, K. N., Reid, H. H., Borg, N. A., Broughton, S. E., Huyton, T., Anderson, R. P., McCluskey, J. & Rossjohn, J. 2007. The production and crystallization of the human leukocyte antigen class II molecules HLA-DQ2 and HLA-DQ8 complexed with deamidated gliadin peptides implicated in coeliac disease. *Acta Crystallogr Sect F Struct Biol Cryst Commun*, 63, 1021-5.
- Hidalgo, H., Kallweit, U., Mathis, J. & Bassetti, C. L. 2016. Post Tick-Borne Encephalitis Virus Vaccination Narcolepsy with Cataplexy. *Sleep*, 39, 1811-1814.
- Hintzen, R. Q., De Jong, R., Lens, S. M. & Van Lier, R. A. 1994. CD27: marker and mediator of T-cell activation? *Immunol Today*, 15, 307-11.
- Höhl, T., Pezzotti, N., Van Unen, V., Koning, F., Eisemann, E., Lelieveldt, B. & Vilanova, A. 2016. Cytosplore: Interactive Immune Cell Phenotyping for Large Single-Cell Datasets. *Computer Graphics Forum*, 35, 171-180.
- Hong, S. C., Lin, L., Lo, B., Jeong, J. H., Shin, Y. K., Kim, S. Y., Kweon, Y., Zhang, J., Eiden, M., Smith, A., Hansen, J., Grumet, F. C. & Mignot, E. 2007. DQB1*0301 and DQB1*0601 modulate narcolepsy susceptibility in Koreans. *Hum Immunol*, 68, 59-68.
- Hor, H., Kutalik, Z., Dauvilliers, Y., Valsesia, A., Lammers, G. J., Donjacour, C. E., Iranzo, A., Santamaria, J., Peraita Adrados, R., Vicario, J. L., Overeem, S., Arnulf, I., Theodorou, I., Jennum, P., Knudsen, S., Bassetti, C., Mathis, J., Lecendreux, M., Mayer, G., Geisler, P., Beneto, A., Petit, B., Pfister, C., Burki, J. V., Didelot, G., Billiard, M., Ercilla, G., Verduijn, W., Claas, F. H., Vollenweider, P., Waerber, G., Waterworth, D. M., Mooser, V., Heinzer, R., Beckmann, J. S., Bergmann, S. & Tafti, M. 2010. Genome-wide association study identifies new HLA class II haplotypes strongly protective against narcolepsy. *Nat Genet*, 42, 786-9.
- Husain, A. M., Ristanovic, R. K. & Bogan, R. K. 2009. Weight loss in narcolepsy patients treated with sodium oxybate. *Sleep Med*, 10, 661-3.
- Icsd 2005. *International Classification of Sleep Disorders, 2nd edition*, Darien, IL, USA, American Academy of Sleep Disorders.
- Icsd 2014. *International Classification of Sleep Disorders, 3rd edition*, Darien, IL, USA, American Academy of Sleep Disorders.
- Jiang, W., Birtley, J. R., Hung, S. C., Wang, W., Chiou, S. H., Macaubas, C., Kornum, B., Tian, L., Huang, H., Adler, L., Weaver, G., Lu, L., Ilstad-Minnihan, A., Somasundaram, S., Ayyangar, S., Davis, M. M., Stern, L. J. & Mellins, E. D. 2019. In vivo clonal expansion and phenotypes of hypocretin-specific CD4(+) T cells in narcolepsy patients and controls. *Nat Commun*, 10, 5247.
- Johns, M. W. 1992. Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep*, 15, 376-81.
- Juji, T., Satake, M., Honda, Y. & Doi, Y. 1984. HLA antigens in Japanese patients with narcolepsy. All the patients were DR2 positive. *Tissue Antigens*, 24, 316-9.
- Juvodden, H. T., Alnaes, D., Lund, M. J., Agartz, I., Andreassen, O. A., Dietrichs, E., Thorsby, P. M., Westlye, L. T. & Knudsen, S. 2018. Widespread white matter changes in post-H1N1 patients with narcolepsy type 1 and first-degree relatives. *Sleep*, 41.
- Juvodden, H. T., Alnaes, D., Lund, M. J., Dietrichs, E., Thorsby, P. M., Westlye, L. T. & Knudsen, S. 2019a. Hypocretin-deficient narcolepsy patients have abnormal brain activation during humor processing. *Sleep*.
- Juvodden, H. T., Viken, M. K., Nordstrand, S. E. H., Viste, R., Westlye, L. T., Thorsby, P. M., Lie, B. A. & Knudsen-Heier, S. 2019b. HLA and sleep parameter associations in post-H1N1 narcolepsy type 1 patients and first-degree relatives. *Sleep*.
- Kabsch, W. 2010. XDS. *Acta Crystallogr D Biol Crystallogr*, 66, 125-32.

- Kanbayashi, T., Inoue, Y., Chiba, S., Aizawa, R., Saito, Y., Tsukamoto, H., Fujii, Y., Nishino, S. & Shimizu, T. 2002. CSF hypocretin-1 (orexin-A) concentrations in narcolepsy with and without cataplexy and idiopathic hypersomnia. *J Sleep Res*, 11, 91-3.
- Kooy-Winkelaar, Y. & Koning, F. 2015. Isolation and Cloning of Gluten-Specific T Cells in Celiac Disease. *Methods Mol Biol*, 1326, 53-9.
- Kornum, B. R., Burgdorf, K. S., Holm, A., Ullum, H., Jennum, P. & Knudsen, S. 2017a. Absence of autoreactive CD4(+) T-cells targeting HLA-DQA1*01:02/DQB1*06:02 restricted hypocretin/orexin epitopes in narcolepsy type 1 when detected by EliSpot. *J Neuroimmunol*, 309, 7-11.
- Kornum, B. R., Kawashima, M., Faraco, J., Lin, L., Rico, T. J., Hesselson, S., Axtell, R. C., Kuipers, H., Weiner, K., Hamacher, A., Kassack, M. U., Han, F., Knudsen, S., Li, J., Dong, X., Winkelmann, J., Plazzi, G., Nevsimalova, S., Hong, S. C., Honda, Y., Honda, M., Hogl, B., Ton, T. G., Montplaisir, J., Bourgin, P., Kemlink, D., Huang, Y. S., Warby, S., Einen, M., Eshragh, J. L., Miyagawa, T., Desautels, A., Ruppert, E., Hesla, P. E., Poli, F., Pizza, F., Frauscher, B., Jeong, J. H., Lee, S. P., Strohl, K. P., Longstreth, W. T., Jr., Kvale, M., Dobrovolna, M., Ohayon, M. M., Nepom, G. T., Wichmann, H. E., Rouleau, G. A., Gieger, C., Levinson, D. F., Gejman, P. V., Meitinger, T., Peppard, P., Young, T., Jennum, P., Steinman, L., Tokunaga, K., Kwok, P. Y., Risch, N., Hallmayer, J. & Mignot, E. 2011. Common variants in P2RY11 are associated with narcolepsy. *Nat Genet*, 43, 66-71.
- Kornum, B. R., Knudsen, S., Ollila, H. M., Pizza, F., Jennum, P. J., Dauvilliers, Y. & Overeem, S. 2017b. Narcolepsy. *Nat Rev Dis Primers*, 3, 16100.
- Kubota, H., Kanbayashi, T., Tanabe, Y., Ito, M., Takanashi, J., Kohno, Y. & Shimizu, T. 2003. Decreased cerebrospinal fluid hypocretin-1 levels near the onset of narcolepsy in 2 prepubertal children. *Sleep*, 26, 555-7.
- Lammers, G. J., Pijl, H., Iestra, J., Langius, J. A., Buunk, G. & Meinders, A. E. 1996. Spontaneous food choice in narcolepsy. *Sleep*, 19, 75-6.
- Latorre, D., Kallweit, U., Armentani, E., Foglierini, M., Mele, F., Cassotta, A., Jovic, S., Jarrossay, D., Mathis, J., Zellini, F., Becher, B., Lanzavecchia, A., Khatami, R., Manconi, M., Tafti, M., Bassetti, C. L. & Sallusto, F. 2018. T cells in patients with narcolepsy target self-antigens of hypocretin neurons. *Nature*.
- Lecendreux, M., Churlaud, G., Pitoiset, F., Regnault, A., Tran, T. A., Liblau, R., Klatzmann, D. & Rosenzweig, M. 2017. Narcolepsy Type 1 Is Associated with a Systemic Increase and Activation of Regulatory T Cells and with a Systemic Activation of Global T Cells. *PLoS One*, 12, e0169836.
- Lin, L., Faraco, J., Li, R., Kadotani, H., Rogers, W., Lin, X., Qiu, X., De Jong, P. J., Nishino, S. & Mignot, E. 1999. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. *Cell*, 98, 365-76.
- Lind, A., Akel, O., Wallenius, M., Ramelius, A., Maziarz, M., Zhao, L. P., Geraghty, D. E., Palm, L., Lernmark, A. & Larsson, H. E. 2019. HLA high-resolution typing by next-generation sequencing in Pandemrix-induced narcolepsy. *PLoS One*, 14, e0222882.
- Lind, A., Freyhult, E., Ramelius, A., Olsson, T., Arnheim-Dahlstrom, L., Lamb, F., Khademi, M., Ambati, A., Macurer, M., Lima Bomfim, I., Fink, K., Fex, M., Torn, C., Elding Larsson, H. & Lernmark, A. 2017. Antibody Affinity Against 2009 A/H1N1 Influenza and Pandemrix Vaccine Nucleoproteins Differs Between Childhood Narcolepsy Patients and Controls. *Viral Immunol*, 30, 590-600.
- Lind, A., Ramelius, A., Olsson, T., Arnheim-Dahlstrom, L., Lamb, F., Khademi, M., Ambati, A., Macurer, M., Nilsson, A. L., Bomfim, I. L., Fink, K. & Lernmark, A. 2014. A/H1N1 antibodies and TRIB2 autoantibodies in narcolepsy patients diagnosed in conjunction with the Pandemrix vaccination campaign in Sweden 2009-2010. *J Autoimmun*, 50, 99-106.
- Lind, A., Salami, F., Landtblom, A. M., Palm, L., Lernmark, A., Adolfsson, J. & Larsson, H. E. 2020. Immunocyte single cell analysis of vaccine-induced narcolepsy. *Eur J Immunol*.
- Littner, M. R., Kushida, C., Wise, M., Davila, D. G., Morgenthaler, T., Lee-Chiong, T., Hirshkowitz, M., Daniel, L. L., Bailey, D., Berry, R. B., Kapen, S. & Kramer, M. 2005. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep*, 28, 113-21.
- Liu, J., Merkle, F. T., Gandhi, A. V., Gagnon, J. A., Woods, I. G., Chiu, C. N., Shimogori, T., Schier, A. F. & Prober, D. A. 2015. Evolutionarily conserved regulation of hypocretin neuron specification by Lhx9. *Development*, 142, 1113-24.
- Liu, S. Y., Perez, M. A. & Lau, N. 2018. The impact of sleep disorders on driving safety-findings from the Second Strategic Highway Research Program naturalistic driving study. *Sleep*, 41.

- Lopes, D. A., Coelho, F. M., Pradella-Hallinan, M., De Araujo Melo, M. H. & Tufik, S. 2015. Infancy narcolepsy: Streptococcus infection as a causal factor. *Sleep Sci*, 8, 49-52.
- Lopez, R., Barateau, L., Evangelista, E. & Dauvilliers, Y. 2017. Depression and Hypersomnia: A Complex Association. *Sleep Med Clin*, 12, 395-405.
- Luo, G., Ambati, A., Lin, L., Bonvalet, M., Partinen, M., Ji, X., Maecker, H. T. & Mignot, E. J. 2018. Autoimmunity to hypocretin and molecular mimicry to flu in type 1 narcolepsy. *Proc Natl Acad Sci U S A*, 115, E12323-e12332.
- Luo, G., Lin, L., Jacob, L., Bonvalet, M., Ambati, A., Plazzi, G., Pizza, F., Leib, R., Adams, C. M., Partinen, M. & Mignot, E. J. 2017. Absence of anti-hypocretin receptor 2 autoantibodies in post pandemrix narcolepsy cases. *PLoS One*, 12, e0187305.
- Madden, C. J., Tupone, D. & Morrison, S. F. 2012. Orexin modulates brown adipose tissue thermogenesis. *Biomol Concepts*, 3, 381-386.
- Maes, J., Verbraecken, J., Willemen, M., De Volder, I., Van Gastel, A., Michiels, N., Verbeek, I., Vandekerckhove, M., Wuyts, J., Haex, B., Willemen, T., Exadaktylos, V., Bulckaert, A. & Cluydts, R. 2014. Sleep misperception, EEG characteristics and autonomic nervous system activity in primary insomnia: a retrospective study on polysomnographic data. *Int J Psychophysiol*, 91, 163-71.
- Mantel, N. 1963. Chi-Square Tests with One Degree of Freedom; Extensions of the Mantel-Haenszel Procedure. *Journal of the American Statistical Association*, 58, 690-700.
- Mantel, N. & Haenszel, W. 1959. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*, 22, 719-48.
- Marti, I., Valko, P. O., Khatami, R., Bassetti, C. L. & Baumann, C. R. 2009. Multiple sleep latency measures in narcolepsy and behaviourally induced insufficient sleep syndrome. *Sleep Med*, 10, 1146-50.
- Mccoy, A. J., Grosse-Kunstleve, R. W., Adams, P. D., Winn, M. D., Storoni, L. C. & Read, R. J. 2007. Phaser crystallographic software. *J Appl Crystallogr*, 40, 658-674.
- Mercer, J. D., Bootzin, R. R. & Lack, L. C. 2002. Insomniacs' perception of wake instead of sleep. *Sleep*, 25, 564-71.
- Mereckiene, J., Cotter, S., Weber, J. T., Nicoll, A., D'ancona, F., Lopalco, P. L., Johansen, K., Wasley, A. M., Jorgensen, P., Levy-Bruhl, D., Giambi, C., Stefanoff, P., Dematte, L. & O'flanagan, D. 2012. Influenza A(H1N1)pdm09 vaccination policies and coverage in Europe. *Euro Surveill*, 17.
- Mickelsen, L. E., Kolling, F. W. T., Chimileski, B. R., Fujita, A., Norris, C., Chen, K., Nelson, C. E. & Jackson, A. C. 2017. Neurochemical Heterogeneity Among Lateral Hypothalamic Hypocretin/Orexin and Melanin-Concentrating Hormone Neurons Identified Through Single-Cell Gene Expression Analysis. *eNeuro*, 4.
- Middelkoop, H. A., Lammers, G. J., Van Hilten, B. J., Ruwhof, C., Pijl, H. & Kamphuisen, H. A. 1995. Circadian distribution of motor activity and immobility in narcolepsy: assessment with continuous motor activity monitoring. *Psychophysiology*, 32, 286-91.
- Mignot, E., Ambati, A. & Luo, G. 2019. Response to "H1N1 hemagglutinin-specific HLA-DQ6-restricted CD4+ T cells can be readily detected in narcolepsy type 1 patients and healthy controls". *J Neuroimmunol*, 333, 476959.
- Mignot, E., Hayduk, R., Black, J., Grumet, F. C. & Guilleminault, C. 1997. HLA DQB1*0602 is associated with cataplexy in 509 narcoleptic patients. *Sleep*, 20, 1012-20.
- Mignot, E., Lammers, G. J., Ripley, B., Okun, M., Nevsimanova, S., Overeem, S., Vankova, J., Black, J., Harsh, J., Bassetti, C., Schrader, H. & Nishino, S. 2002. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch Neurol*, 59, 1553-62.
- Mignot, E., Lin, L., Rogers, W., Honda, Y., Qiu, X., Lin, X., Okun, M., Hohjoh, H., Miki, T., Hsu, S., Leffell, M., Grumet, F., Fernandez-Vina, M., Honda, M. & Risch, N. 2001. Complex HLA-DR and -DQ interactions confer risk of narcolepsy-cataplexy in three ethnic groups. *Am J Hum Genet*, 68, 686-99.
- Mignot, E., Lin, X., Arrigoni, J., Macaubas, C., Olive, F., Hallmayer, J., Underhill, P., Guilleminault, C., Dement, W. C. & Grumet, F. C. 1994. DQB1*0602 and DQA1*0102 (DQ1) are better markers than DR2 for narcolepsy in Caucasian and black Americans. *Sleep*, 17, S60-7.

- Miller, E., Hoshler, K., Hardelid, P., Stanford, E., Andrews, N. & Zambon, M. 2010. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. *Lancet*, 375, 1100-8.
- Mills, E. L., Pierce, K. A., Jedrychowski, M. P., Garrity, R., Winther, S., Vidoni, S., Yoneshiro, T., Spinelli, J. B., Lu, G. Z., Kazak, L., Banks, A. S., Haigis, M. C., Kajimura, S., Murphy, M. P., Gygi, S. P., Clish, C. B. & Chouchani, E. T. 2018. Accumulation of succinate controls activation of adipose tissue thermogenesis. *Nature*, 560, 102-106.
- Moon, H. J., Song, M. L. & Cho, Y. W. 2015. Clinical Characteristics of Primary Insomniacs with Sleep-State Misperception. *J Clin Neurol*, 11, 358-63.
- Moresco, M., Lecciso, M., Ocadlikova, D., Filardi, M., Melzi, S., Kornum, B. R., Antelmi, E., Pizza, F., Mignot, E., Curti, A. & Plazzi, G. 2018. Flow cytometry analysis of T-cell subsets in cerebrospinal fluid of narcolepsy type 1 patients with long-lasting disease. *Sleep Med*, 44, 53-60.
- Murer, T., Imbach, L. L., Hackius, M., Taddei, R. N., Werth, E., Poryazova, R., Gavrilov, Y. V., Winkler, S., Waldvogel, D., Baumann, C. R. & Valko, P. O. 2017. Optimizing MSLT Specificity in Narcolepsy With Cataplexy. *Sleep*, 40.
- Nam, H., Lim, J. S., Kim, J. S., Lee, K. J., Koo, D. L. & Lee, C. 2016. Sleep Perception in Obstructive Sleep Apnea: A Study Using Polysomnography and the Multiple Sleep Latency Test. *J Clin Neurol*, 12, 230-5.
- Natarajan, N., Jain, S. V., Chaudhry, H., Hallinan, B. E. & Simakajornboon, N. 2013. Narcolepsy-cataplexy: is streptococcal infection a trigger? *J Clin Sleep Med*, 9, 269-70.
- Ng, M. C. & Bianchi, M. T. 2014. Sleep misperception in persons with epilepsy. *Epilepsy Behav*, 36, 9-11.
- Nishino, S., Ripley, B., Overeem, S., Lammers, G. J. & Mignot, E. 2000a. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet*, 355, 39-40.
- Nishino, S., Ripley, B., Overeem, S., Lammers, G. J. & Mignot, E. 2000b. Hypocretin (orexin) deficiency in human narcolepsy. *The Lancet*, 355, 39-40.
- Nishino, S., Ripley, B., Overeem, S., Nevsimalova, S., Lammers, G. J., Vankova, J., Okun, M., Rogers, W., Brooks, S. & Mignot, E. 2001. Low cerebrospinal fluid hypocretin (Orexin) and altered energy homeostasis in human narcolepsy. *Ann Neurol*, 50, 381-8.
- Nordstrand, S. E. H., Hansen, B. H., Rootwelt, T., Karlsen, T. I., Swanson, D., Nilsen, K. B. & Knudsen, S. 2019a. Psychiatric symptoms in patients with post-H1N1 narcolepsy type 1 in Norway. *Sleep*, 42.
- Nordstrand, S. E. H., Juvodden, H. T., Viste, R., Rootwelt, T., Karlsen, T. I., Thorsby, P. M., Swanson, D., Nilsen, K. B., Hansen, B. H. & Knudsen-Heier, S. 2019b. Obesity and other medical comorbidities among NT1 patients after the Norwegian H1N1 influenza epidemic and vaccination campaign. *Sleep*.
- Nordstrand, S. H., Hansen, B. H., Kamaleri, Y., Nilsen, K. B., Rootwelt, T., Karlsen, T. I. & Knudsen, S. 2018. Changes in quality of life in individuals with narcolepsy type 1 after the H1N1-influenza epidemic and vaccination campaign in Norway: a two-year prospective cohort study. *Sleep Med*, 50, 175-180.
- Ohayon, M. M., Priest, R. G., Zulley, J., Smirne, S. & Paiva, T. 2002. Prevalence of narcolepsy symptomatology and diagnosis in the European general population. *Neurology*, 58, 1826-33.
- Ollila, H. M., Ravel, J. M., Han, F., Faraco, J., Lin, L., Zheng, X., Plazzi, G., Dauvilliers, Y., Pizza, F., Hong, S. C., Jennum, P., Knudsen, S., Kornum, B. R., Dong, X. S., Yan, H., Hong, H., Coquillard, C., Mahlios, J., Jolanki, O., Einen, M., Arnulf, I., Hogl, B., Frauscher, B., Crowe, C., Partinen, M., Huang, Y. S., Bourgin, P., Vaarala, O., Desautels, A., Montplaisir, J., Mack, S. J., Mindrinos, M., Fernandez-Vina, M. & Mignot, E. 2015. HLA-DPB1 and HLA class I confer risk of and protection from narcolepsy. *Am J Hum Genet*, 96, 136-46.
- Ooi, J. D., Petersen, J., Tan, Y. H., Huynh, M., Willett, Z. J., Ramarathinam, S. H., Eggenhuizen, P. J., Loh, K. L., Watson, K. A., Gan, P. Y., Alikhan, M. A., Dudek, N. L., Handel, A., Hudson, B. G., Fugger, L., Power, D. A., Holt, S. G., Coates, P. T., Gregersen, J. W., Purcell, A. W., Holdsworth, S. R., La Gruta, N. L., Reid, H. H., Rossjohn, J. & Kitching, A. R. 2017. Dominant protection from HLA-linked autoimmunity by antigen-specific regulatory T cells. *Nature*, 545, 243-247.
- Overeem, S., Verschuuren, J. J., Fronczek, R., Schreurs, L., Den Hertog, H., Hegeman-Kleinn, I. M., Van Duinen, S. G., Unmehopa, U. A., Swaab, D. F. & Lammers, G. J. 2006. Immunohistochemical screening for autoantibodies against lateral hypothalamic neurons in human narcolepsy. *J Neuroimmunol*, 174, 187-91.

- Partinen, M., Saarenpää-Heikkilä, O., Ilveskoski, I., Hublin, C., Linna, M., Olsen, P., Nokelainen, P., Alen, R., Wallden, T., Espo, M., Rusanen, H., Olme, J., Satila, H., Arikka, H., Kaipainen, P., Julkunen, I. & Kirjavainen, T. 2012. Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland. *PLoS One*, 7, e33723.
- Pedersen, N. W., Holm, A., Kristensen, N. P., Bjerregaard, A. M., Bentzen, A. K., Marquard, A. M., Tamhane, T., Burgdorf, K. S., Ullum, H., Jennum, P., Knudsen, S., Hadrup, S. R. & Kornum, B. R. 2019. CD8(+) T cells from patients with narcolepsy and healthy controls recognize hypocretin neuron-specific antigens. *Nat Commun*, 10, 837.
- Pelin, Z., Guilleminault, C., Risch, N., Grumet, F. C. & Mignot, E. 1998. HLA-DQB1*0602 homozygosity increases relative risk for narcolepsy but not disease severity in two ethnic groups. US Modafinil in Narcolepsy Multicenter Study Group. *Tissue Antigens*, 51, 96-100.
- Petersen, J., Montserrat, V., Mujico, J. R., Loh, K. L., Beringer, D. X., Van Lummel, M., Thompson, A., Mearin, M. L., Schweizer, J., Kooy-Winkelaar, Y., Van Bergen, J., Drijfhout, J. W., Kan, W. T., La Gruta, N. L., Anderson, R. P., Reid, H. H., Koning, F. & Rossjohn, J. 2014. T-cell receptor recognition of HLA-DQ2-gliadin complexes associated with celiac disease. *Nat Struct Mol Biol*, 21, 480-8.
- Peyron, C., Faraco, J., Rogers, W., Ripley, B., Overeem, S., Charnay, Y., Nevsimalova, S., Aldrich, M., Reynolds, D., Albin, R., Li, R., Hungs, M., Pedrazzoli, M., Padigaru, M., Kucherlapati, M., Fan, J., Maki, R., Lammers, G. J., Bouras, C., Kucherlapati, R., Nishino, S. & Mignot, E. 2000. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat Med*, 6, 991-7.
- Picchioni, D., Hope, C. R. & Harsh, J. R. 2007. A case-control study of the environmental risk factors for narcolepsy. *Neuroepidemiology*, 29, 185-92.
- Plazzi, G., Moghadam, K. K., Maggi, L. S., Donadio, V., Vetrugno, R., Liguori, R., Zoccoli, G., Poli, F., Pizza, F., Pagotto, U. & Ferri, R. 2011. Autonomic disturbances in narcolepsy. *Sleep Med Rev*, 15, 187-96.
- Poli, F., Plazzi, G., Di Dalmazi, G., Ribichini, D., Vicennati, V., Pizza, F., Mignot, E., Montagna, P., Pasquali, R. & Pagotto, U. 2009. Body mass index-independent metabolic alterations in narcolepsy with cataplexy. *Sleep*, 32, 1491-7.
- Ponziani, V., Gennari, M., Pizza, F., Balsamo, A., Bernardi, F. & Plazzi, G. 2016. Growing Up with Type 1 Narcolepsy: Its Anthropometric and Endocrine Features. *J Clin Sleep Med*, 12, 1649-1657.
- Postiglione, E., Antelmi, E., Pizza, F., Lecendreux, M., Dauvilliers, Y. & Plazzi, G. 2018. The clinical spectrum of childhood narcolepsy. *Sleep Med Rev*, 38, 70-85.
- Qiao, S. W., Christophersen, A., Lundin, K. E. & Sollid, L. M. 2014. Biased usage and preferred pairing of alpha- and beta-chains of TCRs specific for an immunodominant gluten epitope in coeliac disease. *Int Immunol*, 26, 13-9.
- Ramberger, M., Hög, B., Stefani, A., Mitterling, T., Reindl, M. & Lutterotti, A. 2017. CD4+ T-Cell Reactivity to Orexin/Hypocretin in Patients With Narcolepsy Type 1. *Sleep*, 40.
- Ripley, B., Overeem, S., Fujiki, N., Nevsimalova, S., Uchino, M., Yesavage, J., Di Monte, D., Dohi, K., Melberg, A., Lammers, G. J., Nishida, Y., Roelandse, F. W., Hungs, M., Mignot, E. & Nishino, S. 2001. CSF hypocretin/orexin levels in narcolepsy and other neurological conditions. *Neurology*, 57, 2253-8.
- Rogers, N. H., Landa, A., Park, S. & Smith, R. G. 2012. Aging leads to a programmed loss of brown adipocytes in murine subcutaneous white adipose tissue. *Aging Cell*, 11, 1074-83.
- Romanov, R. A., Zeisel, A., Bakker, J., Girach, F., Hellysaz, A., Tomer, R., Alpar, A., Mulder, J., Clotman, F., Keimpema, E., Hsueh, B., Crow, A. K., Martens, H., Schwindling, C., Calvigioni, D., Bains, J. S., Mate, Z., Szabo, G., Yanagawa, Y., Zhang, M. D., Rendeiro, A., Farlik, M., Uhlen, M., Wulff, P., Bock, C., Broberger, C., Deisseroth, K., Hokfelt, T., Linnarsson, S., Horvath, T. L. & Harkany, T. 2017. Molecular interrogation of hypothalamic organization reveals distinct dopamine neuronal subtypes. *Nat Neurosci*, 20, 176-188.
- Ruoff, C. M., Reaven, N. L., Funk, S. E., Mcgaughey, K. J., Ohayon, M. M., Guilleminault, C. & Black, J. 2017. High Rates of Psychiatric Comorbidity in Narcolepsy: Findings From the Burden of Narcolepsy Disease (BOND) Study of 9,312 Patients in the United States. *J Clin Psychiatry*, 78, 171-176.

- Saariaho, A. H., Vuorela, A., Freitag, T. L., Pizza, F., Plazzi, G., Partinen, M., Vaarala, O. & Meri, S. 2015. Autoantibodies against ganglioside GM3 are associated with narcolepsy-cataplexy developing after Pandemrix vaccination against 2009 pandemic H1N1 type influenza virus. *J Autoimmun*, 63, 68-75.
- Sakurai, T., Amemiya, A., Ishii, M., Matsuzaki, I., Chemelli, R. M., Tanaka, H., Williams, S. C., Richardson, J. A., Kozlowski, G. P., Wilson, S., Arch, J. R., Buckingham, R. E., Haynes, A. C., Carr, S. A., Annan, R. S., McNulty, D. E., Liu, W. S., Terrett, J. A., Elshourbagy, N. A., Bergsma, D. J. & Yanagisawa, M. 1998. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell*, 92, 573-85.
- Sarkanen, T., Alakuijala, A. & Partinen, M. 2016. Clinical course of H1N1-vaccine-related narcolepsy. *Sleep Med*, 19, 17-22.
- Sarkanen, T. O., Alakuijala, A. P. E., Dauvilliers, Y. A. & Partinen, M. M. 2018. Incidence of narcolepsy after H1N1 influenza and vaccinations: Systematic review and meta-analysis. *Sleep Med Rev*, 38, 177-186.
- Savvidou, A., Knudsen, S., Olsson-Engman, M., Gammeltoft, S., Jennum, P. & Palm, L. 2013. Hypocretin deficiency develops during onset of human narcolepsy with cataplexy. *Sleep*, 36, 147-8.
- Schinkelshoek, M. S., Fronczek, R., Kooy-Winkelaar, E. M. C., Petersen, J., Reid, H. H., Van Der Heide, A., Drijfhout, J. W., Rossjohn, J., Lammers, G. J. & Koning, F. 2019. H1N1 hemagglutinin-specific HLA-DQ6-restricted CD4+ T cells can be readily detected in narcolepsy type 1 patients and healthy controls. *J Neuroimmunol*, 332, 167-175.
- Schmitz, F., Kooy-Winkelaar, Y., Wickmeijer, A. S., Brugman, M. H., Mearin, M. L., Mulder, C., Chuva De Sousa Lopes, S., Mummery, C. L., Staal, F. J., Van Bergen, J. & Koning, F. 2016. The composition and differentiation potential of the duodenal intraepithelial innate lymphocyte compartment is altered in coeliac disease. *Gut*, 65, 1269-78.
- Schneider-Helmert, D. 2005. [Reverse sleep state misperception]. *Sleep Med*, 6, 179; author reply 181.
- Schneider-Helmert, D. & Kumar, A. 1995. Sleep, its subjective perception, and daytime performance in insomniacs with a pattern of alpha sleep. *Biol Psychiatry*, 37, 99-105.
- Seifinejad, A., Li, S., Mikhail, C., Vassalli, A., Pradervand, S., Arribat, Y., Pezeshgi Modarres, H., Allen, B., John, R. M., Amati, F. & Tafti, M. 2019. Molecular codes and in vitro generation of hypocretin and melanin concentrating hormone neurons. *Proc Natl Acad Sci U S A*.
- Sellayah, D., Bharaj, P. & Sikder, D. 2011. Orexin is required for brown adipose tissue development, differentiation, and function. *Cell Metab*, 14, 478-90.
- Sellayah, D. & Sikder, D. 2014. Orexin restores aging-related brown adipose tissue dysfunction in male mice. *Endocrinology*, 155, 485-501.
- Šidák, Z. 1967. Rectangular Confidence Regions for the Means of Multivariate Normal Distributions. *Journal of the American Statistical Association*, 62, 626-633.
- Solms, M. 2000. Dreaming and REM sleep are controlled by different brain mechanisms. *Behav Brain Sci*, 23, 843-50; discussion 904-1121.
- Suzuki, H., Uchiyama, M., Tagaya, H., Ozaki, A., Kuriyama, K., Aritake, S., Shibui, K., Tan, X., Kamei, Y. & Kuga, R. 2004. Dreaming during non-rapid eye movement sleep in the absence of prior rapid eye movement sleep. *Sleep*, 27, 1486-90.
- Tafti, M., Hor, H., Dauvilliers, Y., Lammers, G. J., Overeem, S., Mayer, G., Javidi, S., Iranzo, A., Santamaria, J., Peraïta-Adrados, R., Vicario, J. L., Arnulf, I., Plazzi, G., Bayard, S., Poli, F., Pizza, F., Geisler, P., Wierzbicka, A., Bassetti, C. L., Mathis, J., Lecendreux, M., Donjacour, C. E., Van Der Heide, A., Heinzer, R., Haba-Rubio, J., Feketeova, E., Hogg, B., Frauscher, B., Beneto, A., Khatami, R., Canellas, F., Pfister, C., Scholz, S., Billiard, M., Baumann, C. R., Ercilla, G., Verduijn, W., Claas, F. H., Dubois, V., Nowak, J., Eberhard, H. P., Pradervand, S., Hor, C. N., Testi, M., Tiercy, J. M. & Kutalik, Z. 2014. DQB1 locus alone explains most of the risk and protection in narcolepsy with cataplexy in Europe. *Sleep*, 37, 19-25.
- Tafti, M., Lammers, G. J., Dauvilliers, Y., Overeem, S., Mayer, G., Nowak, J., Pfister, C., Dubois, V., Eliaou, J. F., Eberhard, H. P., Liblau, R., Wierzbicka, A., Geisler, P., Bassetti, C. L., Mathis, J., Lecendreux, M., Khatami, R., Heinzer, R., Haba-Rubio, J., Feketeova, E., Baumann, C. R., Kutalik, Z. & Tiercy, J. M. 2016. Narcolepsy-Associated HLA Class I Alleles Implicate Cell-Mediated Cytotoxicity. *Sleep*, 39, 581-7.
- Takano, K., Boddez, Y. & Raes, F. 2016. I sleep with my Mind's eye open: Cognitive arousal and overgeneralization underpin the misperception of sleep. *J Behav Ther Exp Psychiatry*, 52, 157-165.

- Tanaka, S., Honda, Y., Inoue, Y. & Honda, M. 2006. Detection of autoantibodies against hypocretin, hcrt1r, and hcrt2r in narcolepsy: anti-Hcrt system antibody in narcolepsy. *Sleep*, 29, 633-8.
- Thannickal, T. C., Moore, R. Y., Nienhuis, R., Ramanathan, L., Gulyani, S., Aldrich, M., Cornford, M. & Siegel, J. M. 2000. Reduced number of hypocretin neurons in human narcolepsy. *Neuron*, 27, 469-74.
- The U.S. Xyrem® Multicenter Study Group 2003. A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. *Sleep*, 26, 31-5.
- Thebault, S., Waters, P., Snape, M. D., Cottrell, D., Darin, N., Hallbook, T., Huuttoniemi, A., Partinen, M., Pollard, A. J. & Vincent, A. 2015. Neuronal Antibodies in Children with or without Narcolepsy following H1N1-AS03 Vaccination. *PLoS One*, 10, e0129555.
- Trajanovic, N. N., Radivojevic, V., Kaushansky, Y. & Shapiro, C. M. 2007. Positive sleep state misperception - a new concept of sleep misperception. *Sleep Med*, 8, 111-8.
- Van Der Heide, A., Hegeman-Kleinn, I. M., Peeters, E., Lammers, G. J. & Fronczek, R. 2015a. Immunohistochemical screening for antibodies in recent onset type 1 narcolepsy and after H1N1 vaccination. *J Neuroimmunol*, 283, 58-62.
- Van Der Heide, A., Verduijn, W., Haasnoot, G. W., Drabbels, J. J., Lammers, G. J. & Claas, F. H. 2015b. HLA dosage effect in narcolepsy with cataplexy. *Immunogenetics*, 67, 1-6.
- Van Holst, R. J., Janssen, L. K., Van Mierlo, P., Lammers, G. J., Cools, R., Overeem, S. & Aarts, E. 2018. Enhanced food-related responses in the ventral medial prefrontal cortex in narcolepsy type 1. *Sci Rep*, 8, 16391.
- Van Rooijen, D. E., Roelen, D. L., Verduijn, W., Haasnoot, G. W., Huygen, F. J., Perez, R. S., Claas, F. H., Marinus, J., Van Hilten, J. J. & Van Den Maagdenberg, A. M. 2012. Genetic HLA associations in complex regional pain syndrome with and without dystonia. *J Pain*, 13, 784-9.
- Van Unen, V., Holtt, T., Pezzotti, N., Li, N., Reinders, M. J. T., Eisemann, E., Koning, F., Vilanova, A. & Lelieveldt, B. P. F. 2017. Visual analysis of mass cytometry data by hierarchical stochastic neighbour embedding reveals rare cell types. *Nat Commun*, 8, 1740.
- Van Unen, V., Li, N., Molendijk, I., Temurhan, M., Holtt, T., Van Der Meulen-De Jong, A. E., Verspaget, H. W., Mearin, M. L., Mulder, C. J., Van Bergen, J., Lelieveldt, B. P. & Koning, F. 2016. Mass Cytometry of the Human Mucosal Immune System Identifies Tissue- and Disease-Associated Immune Subsets. *Immunity*, 44, 1227-39.
- Vassalli, A., Li, S. & Tafti, M. 2015. Comment on "Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2". *Sci Transl Med*, 7, 314le2.
- Verduyn, W., Doxiadis, I., Anholts, J., Drabbels, J. J., Naipal, A., D'amaro, J., Persijn, G. G., Giphart, M. J. & Schreuder, G. M. 1993. Biotinylated DRB sequence-specific oligonucleotides. Comparison to serologic HLA-DR typing of organ donors in eurotransplant. *Hum Immunol*, 37, 59-67.
- Wang, Z., Wu, H., Stone, W. S., Zhuang, J., Qiu, L., Xu, X., Wang, Y., Zhao, Z., Han, F. & Zhao, Z. 2016. Body weight and basal metabolic rate in childhood narcolepsy: a longitudinal study. *Sleep Med*, 25, 139-144.
- Wijnans, L., Lecomte, C., De Vries, C., Weibel, D., Sammon, C., Hviid, A., Svanstrom, H., Molgaard-Nielsen, D., Heijbel, H., Dahlstrom, L. A., Hallgren, J., Sparen, P., Jennum, P., Mosseveld, M., Schuemie, M., Van Der Maas, N., Partinen, M., Romio, S., Trotta, F., Santuccio, C., Menna, A., Plazzi, G., Moghadam, K. K., Ferro, S., Lammers, G. J., Overeem, S., Johansen, K., Kramarz, P., Bonhoeffer, J. & Sturkenboom, M. C. 2013. The incidence of narcolepsy in Europe: before, during, and after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns. *Vaccine*, 31, 1246-54.
- Zhang, Z., Mayer, G., Dauvilliers, Y., Plazzi, G., Pizza, F., Fronczek, R., Santamaria, J., Partinen, M., Overeem, S., Peraita-Adrados, R., Da Silva, A. M., Sonka, K., Rio-Villegas, R. D., Heinzer, R., Wierzbicka, A., Young, P., Hogl, B., Bassetti, C. L., Manconi, M., Feketeova, E., Mathis, J., Paiva, T., Canellas, F., Lecendreux, M., Baumann, C. R., Barateau, L., Pesenti, C., Antelmi, E., Gaig, C., Iranzo, A., Lillo-Triguero, L., Medrano-Martinez, P., Haba-Rubio, J., Gorban, C., Luca, G., Lammers, G. J. & Khatami, R. 2018. Exploring the clinical features of narcolepsy type 1 versus narcolepsy type 2 from European Narcolepsy Network database with machine learning. *Sci Rep*, 8, 10628.

