



Geneeskundige Stichting Koningin Elisabeth
Fondation Médicale Reine Elisabeth
Königin-Elisabeth-Stiftung für Medizin
Queen Elisabeth Medical Foundation

Publicaties – Publications – Publikationen – Publications

2023–2025

G.S.K.E. – F.M.R.E. – K.E.S.M. – Q.E.M.F.

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Interuniversitaire onderzoeksprojecten
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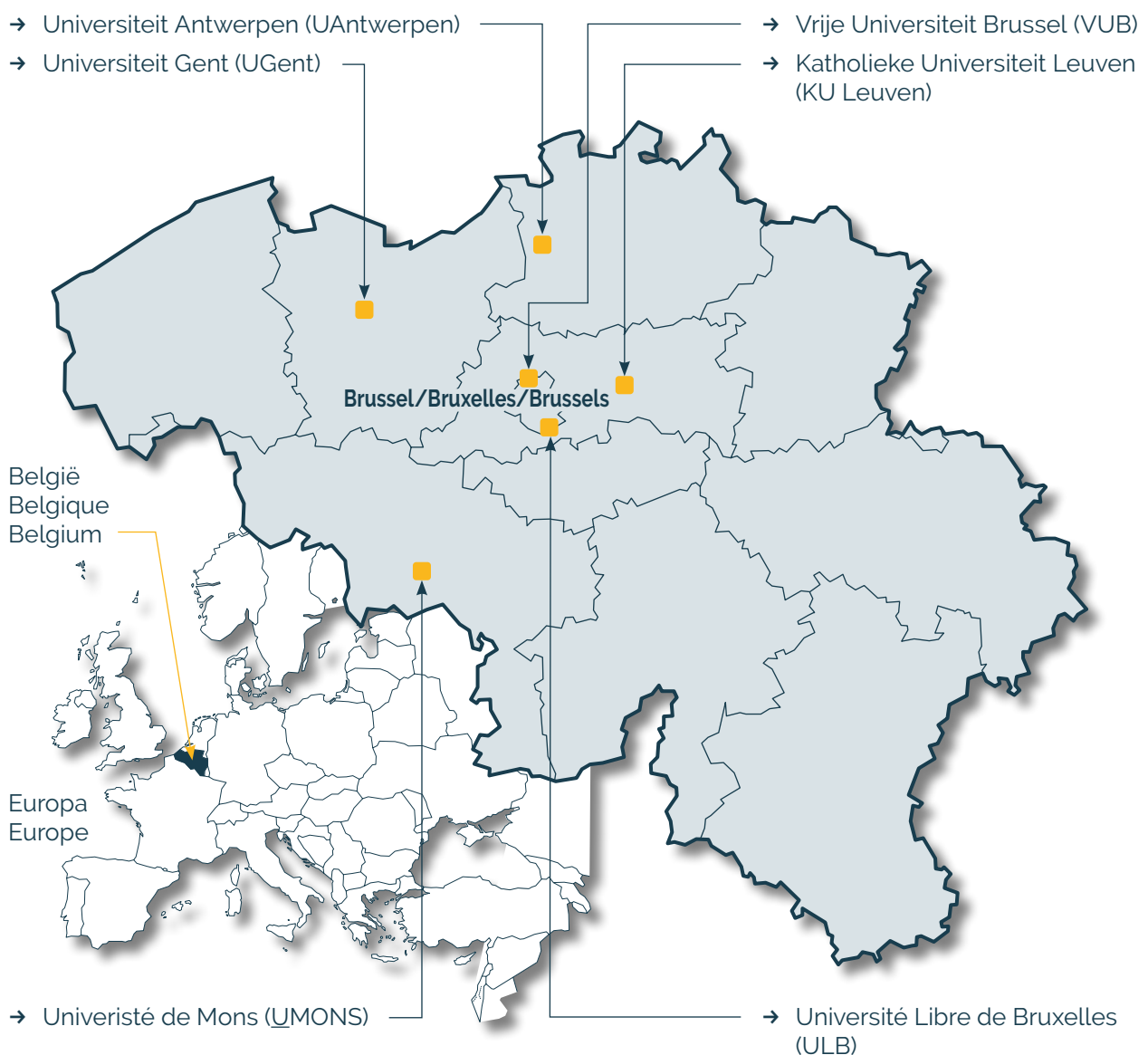
Projets de recherche interuniversitaire
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Universités ayant des programmes de recherche subventionnés par la F.M.R.E.

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Projets de recherche interuniversitaire 2023-2025 subventionnés par la F.M.R.E.

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Prof. dr. Geert Van Loo (UGent)

Prof. Kiavash Movahedi (VUB)

OTULIN in neuroinflammation and Alzheimer pathology

Prof. dr. Sarah Weckhuysen (UAntwerpen)

Prof. dr. Bjorn Menten (UGent)

Detection of somatic mutations and disease-defining methylation patterns in brain tissue and cerebrospinal fluid of patients with non-acquired focal epilepsy

Prof. dr. Renzo Manusco (UAntwerpen)

Prof. dr. Joris De Wit (KU Leuven)

Dissecting the molecular basis of microglia-synapse communication in AD

Prof. dr. Ann Massie (VUB)

Prof. dr. Lutgarde Arckens (KU Leuven)

The xCT-/- killifish to validate the potential of system xc- as therapeutic target in Parkinson's disease

Prof. dr. Karelle Leroy (ULB)

Prof. dr. Laurence Ris (UMONS)

Prof. dr. Kristel Slegers (UAntwerpen)

Involvement of diabetes and antidiabetic treatment on tau pathology propagation



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Publicaties – Publications – Publikationen – Publications

UGent – VUB

Prof. dr. Geert van Loo
Prof. dr. Kiavash Movahedi

Prof. dr. Geert van Loo (UGent)

VIB-UGent Inflammation
Technologiepark 71
9052 Gent-Zwijnaarde
Belgium
T +32-(0)9 3313761
Geert.vanloo@irc.vib-ugent.be

Prof. Kiavash Movahedi (VUB)

Research Center Vrije Universiteit Brussel
Laarbeeklaan 103 building E, room E234
1090 Jette-Brussels
Belgium
T +32-(0)2 4774569
kiavash.movahedi@vub.be

Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- SRINIVASAN, S*, KANCHEVA, D*, DE REN, S*, SAITO, T*, JANS, M., BOONE, F., VANDENDRIESSCHE, C., PAESMANS, I., MAURIN, H., VANDENBROUCKE, R.E., HOSTE, E., VOET, S., SCHEYLTJENS, I., PAVIE, B., LIPPENS, S., SCHWABENLAND, M., PRINZ, M., SAIDO, T., BOTTELBERGS, A+, MOVAHEDI, K+, LAMKANFI, M.+ AND VAN LOO, G+.

Inflammasome signaling is dispensable for β -amyloid-induced neuropathology in preclinical models of Alzheimer's disease.

Frontiers Immunol., in press. (IF : 7.3).

Publication 2024 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- ***Inflammasome signaling is dispensable for β -amyloid-induced neuropathology in preclinical models of Alzheimer's disease.***

Frontiers Immunol: Jan 29;15:1323409. doi: 10.3389/fimmu.2024.1323409 .

eCollection 2024. IF:7.3

Abstract

Background: Alzheimer's disease (AD) is the most common neurodegenerative disorder affecting memory and cognition. The disease is accompanied by an abnormal deposition of β -amyloid plaques in the brain that contributes to neurodegeneration and is known to induce glial inflammation. Studies in the *APP/PS1* mouse model of β -amyloid-induced neuropathology have suggested a role for inflammasome activation in β -amyloid-induced neuroinflammation and neuropathology.

Methods: Here, we evaluated the *in vivo* role of microglia-selective and full body inflammasome signalling in several mouse models of β -amyloid-induced AD neuropathology.

Results: Microglia-specific deletion of the inflammasome regulator A20 and inflammasome effector protease caspase-1 in the *App^{NL-G-F}* and *APP/PS1* models failed to identify a prominent role for microglial inflammasome signalling in β -amyloid-induced neuropathology. Moreover, global inflammasome inactivation through respectively full body deletion of caspases 1 and 11 in *App^{NL-G-F}* mice and *Nlrp3* deletion in *APP/PS1* mice also failed to modulate amyloid pathology and disease progression. In agreement, single-cell RNA sequencing did not reveal an important role for *Nlrp3* signalling in driving microglial activation and the transition into disease-associated states, both during homeostasis and upon amyloid pathology.

Conclusion: Collectively, these results question a generalizable role for inflammasome activation in preclinical amyloid-only models of neuroinflammation.

Keywords: Alzheimer's disease; inflammasome; microglia; neuroinflammation; β -amyloid.

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Elisabeth" (GSKE), the Charcot Foundation, and the "Concerted Research Actions" (GOA) of Ghent University (BOF23/GOA/001). Research in the Lamkanfi lab is supported by Ghent University (BOF23/GOA/001), and by research grants from the FWO (GOI5722N, G017121N, G014221N) and European Research Council (ERC-2022-PoC 101101075). Research in the Saito lab was supported by grants-in-aid for Scientific Research (20H03564) from MEXT, AMED (JP21gm1210010s0102 and JP21dk0207050h001), JST (Moonshot R&D; Grant Number JPMJMS2024), Grant-in-aid for Research in Nagoya City University (Grant Number 2021101), the Hori Sciences & Arts Foundation, and Toyoaki Scholarship Foundation. AB and KM were supported by VLAIO (HBC.2017.0948). GvL and AB were supported by VLAIO (HBC.2020.3240). MS was supported by the Berta-Ottenstein-Programme for Clinician Scientists, Faculty of Medicine, University of Freiburg, and the IMM-PACT-Programme for Clinician Scientists, Department of Medicine II, Medical Center, University of Freiburg and Faculty of Medicine, University of Freiburg, funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation, 413517907).

- PAESMANS, I., VAN KOLEN, K., VANDERMEEREN, M., SHIH, P-Y., WUYTS, D., BOONE, F., GARCIA SANCHEZ, S., GRAUWEN, K., VAN HAUWERMEIREN, F., VAN OPDENBOSCH, N., LAMKANFI, M., VAN LOO, G.+ AND BOTTELBERGS, B.+ (2024)

NLRP3 Inflammasome Activation and Pyroptosis Are Dispensable for Tau Pathology.

Front Aging Neurosci.,16:1459134

+shared last author

Abstract

Background Neuroinflammation is widely recognized as a key factor in the pathogenesis of Alzheimer's disease (AD), alongside β -amyloid deposition and the formation of neurofibrillary tangles. The NLR family pyrin domain containing 3 (NLRP3) inflammasome, part of the innate immune system, has been implicated in the neuropathology of both preclinical amyloid and tau transgenic models. Activation of the NLRP3 pathway involves an initial priming step, which increases the expression of *Nlrp3* and interleukin (IL)-1 β , followed by the assembly of the NLRP3 inflammasome complex, comprising NLRP3, ASC, and caspase-1. This assembly leads to the proteolytic maturation of the pro-inflammatory cytokines IL-1 β and IL-18. Additionally, the NLRP3 inflammasome induces Gasdermin D (GSDMD) cleavage, forming membrane pores through which IL-1 β and IL-18 are secreted. Inhibition of NLRP3 has been shown to enhance plaque clearance by modulating microglial activation. Furthermore, blocking NLRP3 in tau transgenic mice has been found to reduce tau phosphorylation by affecting the activity of certain tau kinases and phosphatases.

Methods: In this study, organotypic brain slice cultures from P301S transgenic mice were treated with lipopolysaccharide (LPS) plus nigericin as a positive control or exposed to tau seeds (K18) to evaluate NLRP3 inflammasome activation. The effect of tau seeding on NLRP3 activity was further examined using Meso Scale Discovery (MSD) assays to measure IL1 β secretion levels in the presence and absence of NLRP3 inhibitors. The role of NLRP3 activity was investigated in full-body *Nlrp3* knockout mice crossbred with the tau transgenic P301S model. Additionally, full-body and microglia-selective *Gsdmd* knockout mice were crossbred with P301S mice, and tau pathology and neurodegeneration were evaluated at early and late stages of the disease using immunohistochemistry and biochemical assays.

Results: Activation of the NLRP3 pathway was observed in the mouse organotypic slice culture (OSC) model following stimulation with LPS and nigericin or exposure to tau seeds. However, *Nlrp3* deficiency did not mitigate tauopathy or neurodegeneration in P301S mice *in vivo*, showing only a minor effect on plasma neurofilament (NF-L) levels. Consistently, *Gsdmd* deficiency did not alter tau pathology in P301S mice. Furthermore, neither

full-body nor microglia-selective *Gsdmd* deletion had an impact on neuronal pathology or the release of pro-inflammatory cytokines.

Conclusion: The absence of key components of the NLRP3 inflammasome pathway did not yield a beneficial effect on tau pathology or neurodegeneration in the preclinical Tau-P301S mouse model of AD. Nonetheless, organotypic slice cultures could serve as a valuable *ex vivo* mechanistic model for evaluating NLRP3 pathway activation and pharmacological inhibitors.

Keywords: GSDMD; NLRP3; OSCs; P301S; neurodegeneration and tau pathology.

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- No publication in 2025



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Publicaties – Publications –
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UAntwerpen – KU Leuven

Prof. dr. Renzo Manusco
Prof. dr. Joris De Wit

Prof. dr. Renzo Manusco (UAntwerpen)

Group Leader

Laboratory of Microglia and Inflammation in Neurological Disorders (MIND)

VIB-Center for Molecular Neurology (CMN), VIB.

Universiteit Antwerpen-CDE, Parking P4, Gebouw V 0.10

Universiteitsplein 1, 2610 Antwerpen

Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- No publication in 2023

Publications in 2024 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- No publication in 2024

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- No publication in 2025

Prof. dr. Joris De Wit (KU Leuven)

Group Leader at VIB-KU Leuven
Center for Brain & Disease Research
Department of Neurosciences
ON5 Herestraat 49 – bus 602, 3000 Leuven

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Publications in 2025 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- VERPOORT B, AMADO L, VANDENSTEEN J, LEYSEN E, DASCENCO D, VANDENBEMPT J, LEMMENS I, WAUMAN J, VENNEKENS K, ESCAMILLA-AYALA A, FREITAS A, VOETS T, MUNCK S, TAVERNIER J, WIERDA K, **DE WIT J** (2025).

A postsynaptic GPR158- PLCXD2 complex controls spine apparatus abundance and dendritic spine maturation.

Developmental Cell 16:S1534-5807(25)00263-1. 10.1016/j.devcel.2025.04.025

IF: 8.7; Q factor: Q1 in Cell Biology

Abstract

The spine apparatus (SA), an endoplasmic reticulum (ER)-related organelle present in a subset of dendritic spines, plays a key role in postsynaptic development and is implicated in various neurological disorders. The molecular mechanisms that dictate SA localization at selected synapses remain elusive. Here, we identify a postsynaptic signaling complex comprising the G protein-coupled receptor (GPCR)- GPR158 and a constitutively active phospholipase C (PLC) family member, PLC X-domain containing 2 (PLCXD2), that controls SA abundance. Sparse genetic manipulations of mouse cortical neurons in vivo demonstrate that, in the absence of GPR158, unrestrained PLCXD2 activity impedes postsynaptic SA incorporation and hampers structural and functional dendritic spine maturation. Extracellular heparan sulfate proteoglycan (HSPG) binding modulates the GPR158-PLCXD2 interaction, providing spatiotemporal control over GPR158 signaling. Together, our findings uncover a direct GPCR-like receptor-to-PLC signaling pathway that bypasses canonical PLC regulation via G proteins. This GPR158-PLCXD2 module regulates SA abundance, essential for proper postsynaptic structure and function.

Keywords: AMPA receptor; ER-PM contact sites; GPCR; dendritic spine; organelle; phospholipase; postsynaptic development; receptor signaling; spine apparatus; synapse.

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Publicaties – Publications –
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ULB – UMONS – UAntwerpen

Prof. dr. Karelle Leroy
Prof. dr. Laurence Ris
Prof. dr. Kristel Slegers

Prof. dr. Karelle Leroy (ULB)

Assistant professor, ULB

Head of the Alzheimer research group in the Laboratory of Histology

<https://alzheimer-research.medecine.ulb.be>

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- No publication in 2023

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- No publication in 2025

Prof. dr. Laurence Ris (UMONS)
Department of Neurosciences

Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

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- No publication in 2024

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- No publication in 2025

Prof. dr. Kristel Sleegers (UAntwerpen)

Professor, UA

Head of the Complex Genetics of

Alzheimer's disease group at VIB – UA Center for Molecular Neurology

<https://uantwerpen.vib.be/group/kristelSleegers>

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- No publication in 2025



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Publicaties – Publications –
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UAntwerpen – UGent

Prof. dr. Sarah Weckhuysen
Prof. dr. Ir. Bjorn Menten

Prof. dr. Sarah Weckhuysen (UAntwerpen)

Applied&Translational Neurogenomics Group VIB-Uantwerp
Center for Molecular Neurology Uantwerp CDE
Parking P4, Building V Universiteitsplein 1, 2610 Antwerpen Belgium
uantwerpen.vib.be

Neurology Department
Antwerp University Hospital
Drie Eikenstraat 655
2650 Edegem
www.UZA.be/neurologie

Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- N. DIRKX, WOUT J. WEURING , E. DE VRIENDT, N. SMAL, J. VAN DE VONDERVOORT, RUBEN VAN 'T SLOT, M. KOETSIER, N. ZONNEKEIN, TIM DE POOTER, S. WECKHUYSEN AND B. P. C. KOELEMAN

Increased prime edit rates in KCNQ2 and SCN1A via single nicking all-in-one plasmids

BMC Biol, 2023 Jul 13;21(1):156. Doi: 10.1186/s12915-023-01646-7.

Abstract

Background Prime editing (PE) is the most recent gene editing technology able to introduce targeted alterations to the genome, including single base pair changes, small insertions, and deletions. Several improvements to the PE machinery have been made in the past few years, and these have been tested in a range of model systems including immortalized cell lines, stem cells, and animal models. While double nicking RNA (dncRNA) PE systems PE3 and PE5 currently show the highest editing rates, they come with reduced accuracy as undesired indels or SNVs arise at edited loci. Here, we aimed to improve single ncRNA (sncRNA) systems PE2 and PE4max by generating novel all-in-one (pAIO) plasmids driven by an EF-1 promoter, which is especially suitable for human-induced pluripotent stem cell (hiPSC) models.

Results pAIO-EF1-PE2 and pAIO-EF1-PE4max were used to edit the voltage gated potassium channel gene KCNQ2 and voltage gated sodium channel gene SCN1A. Two clinically relevant mutations were corrected using pAIO-EF1-PE2 including the homozygous truncating SCN1A R612* variant in HEK293T cells and the heterozygous gain-of-function KCNQ2 R201C variant in patient-derived hiPSC. We show that sncRNA PE yielded detectable editing rates in hiPSC ranging between 6.4% and 9.8%, which was further increased to 41% after a GFP-based fluorescence-activated cell sorting (FACS) cell sorting step. Furthermore, we show that selecting the high GFP expressing population improved editing efficiencies up to 3.2-fold compared to the low GFP expressing population, demonstrating that not only delivery but also the number of copies of the PE enzyme and/or pegRNA per cell are important for efficient editing. Edit rates were not improved when an additional silent protospacer-adjacent motif (PAM)-removing alteration was introduced in hiPSC at the target locus. Finally, there were no genome-wide off-target effects using pAIO-EF1-PE2 and no off-target editing activity near the edit locus highlighting the accuracy of snc prime editors.

Conclusion Taken together, our study shows an improved efficacy of EF-1 driven sncRNA pAIO-PE plasmids in hiPSC reaching high editing rates, especially after FACS sorting. Optimizing these sncRNA PE systems is of high value when considering future therapeutic in vivo use, where accuracy will be extremely important.

Keywords Prime editing, EIEE, CRISPR, SCN1A, KCNQ2, Developmental and epileptic encephalopathy, EF-1 α , Human-induced pluripotent stem cells, Gene editing, Monogenic diseases

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- KATRINE M. JOHANNESSEN | ZEYNEP TÜMER | SARAH WECKHUYSEN | TAHSIN STEFAN BARAKAT | ALLAN BAYAT

Solving the unsolved genetic epilepsies: Current and future perspectives

Epilepsia: 2023 Dec;64(12):3143-3154. – doi: 10.1111/epi.17780. Epub 2023 Oct 17.

Abstract

Many patients with epilepsy undergo exome or genome sequencing as part of a diagnostic workup; however, many remain genetically unsolved. There are various factors that account for negative results in exome/genome sequencing for patients with epilepsy: (1) the underlying cause is not genetic; (2) there is a complex polygenic explanation; (3) the illness is monogenic but the causative gene remains to be linked to a human disorder; (4) family segregation with reduced penetrance; (5) somatic mosaicism or the complexity of, for example, a structural rearrangement; or (6) limited knowledge or diagnostic tools that hinder the proper classification of a variant, resulting in its designation as a variant of unknown significance. The objective of this review is to outline some of the diagnostic options that lie beyond the exome/genome, and that might become clinically relevant within the foreseeable future. These options include: (1) re-analysis of older exome/genome data as knowledge increases or symptoms change; (2) looking for somatic mosaicism or long-read sequencing to detect low-complexity repeat variants or specific structural variants missed by traditional exome/genome sequencing; (3) exploration of the non-coding genome including disruption of topologically associated domains, long range non-coding RNA, or other regulatory elements; and finally (4) transcriptomics, DNA methylation signatures, and metabolomics as complementary diagnostic methods that may be used in the assessment of variants of unknown significance. Some of these tools are currently not integrated into standard diagnostic workup. However, it is reasonable to expect that they will become increasingly available and improve current diagnostic capabilities, thereby enabling precision diagnosis in patients who are currently undiagnosed.

Keywords: DNA methylation; epilepsy; epilepsy genetics; metabolomics; non-coding regions; re-analysis; somatic mosaicism; transcriptomics.

Funding

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- ALLAN BAYAT, STEFANO IAVARONE, FRANCESCO MICELI, ANNE V. JAKOBSEN, KATRINE M., JOHANNESSEN, MARINA NIKANOROVA, RAFAL PLOSKI, KRYSZYNA SZYMANSKA, ROBERT FLAMINI, EDWARD C. COOPER, SARAH WECKHUYSEN, MAURIZIO TAGLIALATELA, RIKKE S. MØLLER

Phenotypic and functional assessment of two novel KCNQ2 gain-of-function variants Y141N and G239S and effects of amitriptyline treatment

Neurotherapeutics: doi: 10.1016/j.neurot.2023.10.006. Epub 2023 Dec 19.

Abstract

While loss-of-function (LoF) variants in KCNQ2 are associated with a spectrum of neonatal-onset epilepsies, gain-of-function (GoF) variants cause a more complex phenotype that precludes neonatal-onset epilepsy. In the present work, the clinical features of three patients

carrying a de novo KCNQ2 Y141N (n 1/4 1) or G239S variant (n 1/4 2) respectively, are described. All three patients had a mild global developmental delay, with prominent language deficits, and strong activation of interictal epileptic activity during sleep. Epileptic seizures were not reported. The absence of neonatal seizures suggested a GoF effect and prompted functional testing of the variants. *In vitro* whole-cell patch-clamp electrophysiological experiments in Chinese Hamster Ovary cells transiently-transfected with the cDNAs encoding Kv7.2 subunits carrying the Y141N or G239S variants in homomeric or heteromeric configurations with Kv7.2 subunits, revealed that currents from channels incorporating mutant subunits displayed increased current densities and hyperpolarizing shifts of about 10 mV in activation gating; both these functional features are consistent with an *in vitro* GoF phenotype. The antidepressant drug amitriptyline induced a reversible and concentration-dependent inhibition of current carried by Kv7.2 Y141N and G239S mutant channels. Based on *in vitro* results, amitriptyline was prescribed in one patient (G239S), prompting a significant improvement in motor, verbal, social, sensory and adaptive behavior skills during the two-year-treatment period. Thus, our results suggest that KCNQ2 GoF variants Y141N and G239S cause a mild DD with prominent language deficits in the absence of neonatal seizures and that treatment with the Kv7 channel blocker amitriptyline might represent a potential targeted treatment for patients with KCNQ2 GoF variants.

Keywords:

Voltage-gated potassium channel Developmental encephalopathy Genotype-phenotype
Amitriptyline
Gain of function

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Publications in 2024 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

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- MATTHIAS DE WACHTER, CHARISSA MILLEVERT, JOOST NICOLAI, ELISABETH CATS, GERHARD KLUGER MATHIEU MILH, ROBIN CLOAREC, STEFFEN SYRBE, KATRIJN ARTS, KATRIEN JANSEN, MAGDALENA KRYGIER, ROBERT SMIGIEL, STEPHANE AUVIN, KERN OLOFSON, CATHRINE ELISABETH GJERULFSEN, BERTEN CEULEMANS¹, RIKKE S. MØLLER, ALLAN BAYAT and **SARAH WECKHUUSEN**,

Amitriptyline use in individuals with KCNQ2/3 gain- of-function variants: A retrospective cohort study

Epilepsia 2025 May;66(5):1628-1640, doi: 10.1111/epi.18310. Epub 2025 Feb 17.

Abstract

Objective: Heterozygous gain- of- function (GOF) variants in *KCNQ2* and *KCNQ3*, encoding the voltage- gated potassium channel subunits Kv7.2 and Kv7.3, lead to neurodevelopmental disorders for which no established treatments are available. Amitriptyline, an antidepressant, blocks Kv7.2/Kv7.3 and has previously been reported to be effective in a single individual with a *KCNQ2* GOF variant. We designed a retrospective, single- arm, multicenter study to investigate the effects of amitriptyline in a real- world setting.

Methods: We used a 7- point Likert scale to measure seizure frequency, clinical examination, motor function, alertness, skill acquisition, communication, mood, behavior, self- care, sleep, tiredness, and electroencephalogram at baseline, after a minimum of 6 weeks of intervention, and, if applicable, after discontinuation.

Adverse events were assessed in all participants, and the effectiveness of the treatment was evaluated in 11 individuals who received a minimum dosage of .5 mg/kg/day for at least 6 weeks. Data were collected from October 2023 to August 2024.

Results: Thirteen individuals, eight with a pathogenic *KCNQ2* GOF variant and five with a pathogenic *KCNQ3* GOF variant, were included. Nine were female, and the median age at start of amitriptyline was 7.1 years (range = 1.5–20 years). Eleven individuals received a minimum dosage of .5 mg/kg/day for at least 6 weeks. The median dosage of amitriptyline administered was 1 mg/kg/day, with a median treatment duration of 29 weeks. Although amitriptyline was ineffective in two individuals (18%), eight (72%) demonstrated at least minimal improvement in two or more domains, with improvements in alertness and communication being the most frequently reported. In those with reported improvements,

Funding

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- NOOR SMAL · CHARISSA MILLEVERT · MATTHIAS DE WACHTER · ELS DE VRIENDT¹, ZAKARIA EDDAFIR · AN-SOFIE SCHOONJANS · ALLAN BAYAT · RIKKE STEENSBJERRE MØLLER · DAVIDE MEI · SIMONA BALESTRINI · RENZO GUERRINI · MARIJE E C MEEUWISSEN · ANNA C JANSEN · SARAH WECKHUYSEN ·

Fibroblast transcriptomics uncovers pathogenic genomic variants in individuals with exome- negative childhood onset epilepsy

Epilepsia 2025 May;66(5):1613-1627. doi: 10.1111/epi.18279. Epub 2025 Jan 29.

Abstract

Objective: This study aims to improve genetic diagnosis in childhood onset epilepsy with neurodevelopmental problems by utilizing RNA sequencing of fibroblasts to identify pathogenic variants that may be missed by exome sequencing and copy number variation analysis.

Methods: We enrolled 41 individuals with childhood onset epilepsy and neurodevelopmental problems who previously had inconclusive genetic testing. Fibroblast samples were cultured and analyzed using RNA sequencing to detect aberrant expression, aberrant splicing, and monoallelic expression using the Detection of RNA Outlier Pipeline (DROP) pipeline. Detected events were correlated with phenotypes, and long-read genome sequencing was performed on individuals with strong candidate events to identify the causal genomic variant. A systematic literature review on RNA sequencing in rare disorders was conducted to contextualize our findings.

Results: RNA sequencing identified five strong candidate events in four individuals, affecting the genes QRICH1, TSC1, SMARCA1, GNAI1, and PTEN. (Likely) pathogenic genomic variants affecting expression of QRICH1, TSC1, and SMARCA1 were detected, resulting in a diagnostic yield of 7% (3/41). Two variants were not covered in the initial exome sequencing data but were revealed through long-read sequencing. The identification of a pathogenic TSC1 variant led to a previously unrecognized diagnosis of tuberous sclerosis complex. This prompted guideline-based screening, which revealed tuberous sclerosis lesions in the brain and lung, directly impacting clinical care. Notably, two of the three pathogenic events would not have been detected using whole blood due to the lack of expression of the involved genes. The lower yield of this study compared to studies in other rare disorders reflects the genetic heterogeneity of epilepsy and neurodevelopmental disorders, and the inaccessibility of affected tissue.

Significance: This research underscores RNA sequencing of cultured fibroblasts as a valuable tool in genetic diagnostics for childhood onset epilepsy, particularly when conventional methods fail. Expanding the control dataset with age-matched samples and incorporating RNA sequencing with nonsense-mediated decay inhibition could further enhance diagnostic yield.

Keywords: RNA sequencing; childhood epilepsy; diagnostics.

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Tracking brain maturation in vivo: functional connectivity, white matter integrity, and synaptic density in developing mice

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Abstract

Background: Investigating dynamic changes during normal brain development is essential for understanding neurodevelopmental disorders (NDDs) and assessing the impact of novel therapies for these conditions. Rodent models, with their shorter developmental timeline, offer a valuable alternative to humans. This study aimed to characterise brain maturation in mice using a longitudinal, multimodal imaging approach.

Methods: We conducted an in vivo imaging study on 31129/Sv mice with a complete longitudinal dataset available for 22 mice. Resting-state functional MRI (rs-fMRI), diffusion tensor imaging (DTI), and [18F]SynVesT-1 PET were used to examine the development of brain functional connectivity (FC), white matter integrity, and synaptic density at three developmental stages: infancy (P14–21), juvenile (P32–42), and adulthood (P87–106).

Findings: From infancy to juvenile age, we observed a significant decrease in FC and synaptic density, alongside increases in fractional anisotropy (FA) and decreases in mean, axial, and radial diffusivity (RD). From juvenile to adult age, synaptic density and FC stabilised, while FA further increased, and RD continued to decrease. The default mode like network was identifiable in mice across all developmental stages

Interpretation: Our findings mirror established patterns of human brain development, with infant mice allowing us to capture critical brain developmental changes, underscoring the translational relevance of our findings. This study provides a robust framework for normal rodent neurodevelopment and establishes a foundation for future research on NDDs in mice and the impact of novel treatments on neurodevelopment.

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Keywords: Neurodevelopment; Resting-state functional magnetic resonance imaging; SV2A; Positron emission tomography; Diffusion tensor imaging

Introduction: Neurodevelopment is a dynamic process involving neurogenesis, synaptogenesis, myelination, and synaptic pruning, which collectively shape neurological pathways and influence brain function.¹ In humans, this process begins around gestational day 26 and continues into adulthood, with a critical period of rapid myelination and syn

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- LIDIA CAROTENUTO, OLIVER KEMINER, GIUSY CARLEO, ANDREA ZALIANI, ANTONIO LEO, RITA CITRARO, GIOVAMBATTISTA DE SARRO, NINA DIRKX, MARCUS KAJI, **SARAH WECKHUYSSEN**, JEANETTE REINSHAGEN, VINCENZO BARRESE, NATASCIA GUIDA, CARMINE OSTACOLO, FRANCESCO MICELI, PHILIP GRIBBON, MAURIZIO TAGLIALATELA

The fast-dissociating D2 antagonist antipsychotic JNJ-37822681 is a neuronal Kv7 channel opener: Potential repurposing for epilepsy treatment

Br J Pharmacol 2025 Nov;182(22):5574-5595. doi: 10.1111/bph.70119. Epub 2025 Jul 23.

Abstract

Background and Purpose: Pharmacological activation of neuronal M-current mediated by Kv7 (Kv7.2–5) potassium channels is a validated mechanism for epilepsy treatment. However, since the market withdrawal of the prototype Kv7 activator retigabine, no Kv7 activator is clinically available for this condition. The object was to identify, characterise and validate new neuronal Kv7 channel activators for epilepsy treatment.

Experimental Approach: A fluorescence-based high-throughput assay was optimised in cells stably expressing Kv7 channels to screen two repurposing libraries including >8000 compounds. Whole-cell patch clamp, in silico docking, mutagenesis and multi-electrode array recordings in human induced-pluripotent stem cell (hiPSCs)-derived cortical-like glutamatergic neurons (iNeurons) were used to evaluate compound(s) potency and efficacy, binding site, and effects on neuronal activity, respective.

Finally, anticonvulsant activity was assessed in two acute seizure models in male mice.

Key Results: JNJ-37822681, a fast-dissociating D2 receptor antagonist in clinical development as antipsychotic, enhanced Kv7.2–5 currents with potency and efficacy largely comparable to retigabine. In Kv7.2 subunits, JNJ-37822681 binding site largely overlapped that for retigabine. In iNeurons, JNJ-37822681 enhanced the M-current, hyperpolarised the resting membrane potential and reduced spontaneous action potential firing. These effects were blocked by the Kv7 antagonist, XE-991, and were not reproduced by the D2 antagonist (-)-sulpiride. Finally, JNJ-37822681 showed anticonvulsant activity in two well-validated mouse models of acute seizures. **Conclusions and Implications:** Our study reveals that JNJ-37822681, which lacks retigabine's potential safety issues due to chemical liability and is already confirmed as safe for human use, represents a potential treatment of Kv7-related neuronal hyperexcitability disorders.

Keywords: antiseizure medications; drug repurposing; epilepsy, Kv7 channels; ion channels; iPSC-derive neurons

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Pathogenic variants in SMARCA1 cause an X-linked neurodevelopmental disorder modulated by NURF complex composition (Upgrade)

Nat Commun. 2025 Nov 10;16(1):9875. doi: 10.1038/s41467-025-64838-5.

Abstract

Pathogenic variants in ATP-dependent chromatin remodeling proteins are a recurrent cause of neurodevelopmental disorders (NDDs). The NURF complex consists of BPTF and either the SMARCA5 or SMARCA1 ISWI-chromatin remodeling enzyme. Pathogenic variants in BPTF and SMARCA5 have been previously implicated in NDDs. Here, we describe 35 individuals from 26 families with de novo or maternally inherited variants in the X-linked SMARCA1 gene. This SMARCA1-related NDD is associated with a spectrum of involvement, including mild to severe ID/DD, delayed or regressive speech development, ASD features, facial dysmorphisms, and other variable features. Individuals carrying SMARCA1 truncating variants exhibit a mildly unique genome-wide DNA methylation profile and a high penetrance of macrocephaly. Genetic dissection of the NURF complex using Smarca1, Smarca5, and Bptf single and double mouse knockouts reveals the importance of NURF composition and dosage for proper forebrain development. We propose that genetic alterations affecting different NURF components, including SMARCA1, result in a NDD with a broad clinical spectrum.

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Risk is influenced by longevity genomics: a polygenic risk score study

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Abstract

Background: Sudden Unexpected Death in Epilepsy (SUDEP) is a rare and tragic outcome in epilepsy, identified by those with the condition as their most serious concern. Although several clinical factors are associated with elevated SUDEP risk, mechanisms underlying SUDEP are poorly understood, making individual risk prediction challenging, especially early in the disease course. We hypothesised that common genetic variation contributes to SUDEP risk.

Methods: Genetic data from people who had succumbed to SUDEP was compared to data from people with epilepsy who had not succumbed to SUDEP and from healthy controls. Polygenic risk scores (PRSs) for longevity, intelligence and epilepsy were compared across cohorts. Reactome pathways and gene ontology terms implicated by the contributing single nucleotide polymorphisms (SNPs) were explored. In the subset of SUDEP cases with the necessary data available, a risk score was calculated using an existing risk prediction tool (SUDEP-3); the added value to this prediction of SNP-based genomic information was evaluated.

Findings: Only European-ancestry participants were included. 161 SUDEP cases were compared to 768 cases with epilepsy and 1153 healthy controls. PRS for longevity was significantly reduced in SUDEP cases compared to disease ($P = 0.0096$) and healthy controls ($P = 0.0016$), as was PRS for intelligence (SUDEP cases compared to disease ($P = 0.0073$) and healthy controls ($P = 0.00024$)). The PRS for epilepsy did not differ between SUDEP cases and disease controls ($P = 0.76$). SNP-determined pathway and gene ontology analysis highlighted those related to inter-neuronal communication as amongst the most enriched in SUDEP. Addition of PRS for longevity and intelligence to SUDEP-3 scores improved risk prediction in a subset of cases (38) and controls (703), raising the area-under-the-curve in a receiver-operator characteristic from 0.699 using SUDEP-3 alone to 0.913 when PRSs were added.

Interpretation: Common genetic variation contributes to SUDEP risk, offering new approaches to improve risk prediction and to understand underlying mechanisms.

Keywords: Death; Epilepsy; Intelligence; Longevity; Risk.

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Prof. dr. ir. Bjorn Menten (UGent)

Lab for Genome Research, Center for Medical Genetics, Department of biomolecular Medicine (UGent)

Associate professor (Faculty of Medicine and Health Sciences, UGent)

Lab supervisor Cytogenomics Laboratory Center for Medical Genetics, UZGent

Lab address: UZ Gent, Medical Research Building 1 (entrance 34), Corneel Heymanslaan, 10, 9000 Gent

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VUB – KU Leuven

Prof. dr. Ann Massie
Prof. dr. Lutgarde Arckens

Prof. dr. Ann Massie (VUB)

Vrije Universiteit Brussel
Center for Neurosciences
Laarbeeklaan 103
1090 Brussels
ann.massie@vub.be
T 02 477 45 02

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Prof. dr. Lutgarde Arckens (KU Leuven)

Katholieke Universiteit Leuven

Department of Biology

Naamsestraat 59

3000 Leuven

lut.arckens@kuleuven.be

T 016/32 39 51

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Prof. dr. Sebastiaan Engelborghs

Vrije Universiteit Brussel (VUB)
Center for Neurosciences (C4N)
Laarbeeklaan 103, 1090 Brussel

Prof. dr. Chris Baeken

Universiteit Gent
Department of Psychiatry & Neuropsychology
C. Heymanslaan 10, 9000 Gent

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Depressive symptoms and amyloid pathology.

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Abstract

Importance: Depressive symptoms are associated with cognitive decline in older individuals. Uncertainty about underlying mechanisms hampers diagnostic and therapeutic efforts. This large-scale study aimed to elucidate the association between depressive symptoms and amyloid pathology.

Objective: To examine the association between depressive symptoms and amyloid pathology and its dependency on age, sex, education, and APOE genotype in older individuals without dementia.

Design, setting, and participants: Cross-sectional analyses were performed using data from the Amyloid Biomarker Study data pooling initiative. Data from 49 research, population-based, and memory clinic studies were pooled and harmonized. The Amyloid Biomarker Study has been collecting data since 2012 and data collection is ongoing. At the time of analysis, 95 centers were included in the Amyloid Biomarker Study. The study included 9746 individuals with normal cognition (NC) and 3023 participants with mild cognitive impairment (MCI) aged between 34 and 100 years for whom data on amyloid biomarkers, presence of depressive symptoms, and age were available. Data were analyzed from December 2022 to February 2024.

Main outcomes and measures: Amyloid-1-42 levels in cerebrospinal fluid or amyloid positron emission tomography scans were used to determine presence or absence of amyloid pathology.

Presence of depressive symptoms was determined on the basis of validated depression rating scale scores, evidence of a current clinical diagnosis of depression, or self-reported depressive symptoms.

Results: In individuals with NC (mean [SD] age, 68.6 [8.9] years; 5664 [58.2%] female; 3002 [34.0%] APOE 4 carriers; 937 [9.6%] had depressive symptoms; 2648 [27.2%] had amyloid pathology), the presence of depressive symptoms was not associated with amyloid pathology (odds ratio [OR], 1.13; 95% CI, 0.90–1.40; $P = .29$). In individuals with MCI (mean [SD] age, 70.2 [8.7] years; 1481 [49.0%] female; 1046 [44.8%] APOE 4 carriers; 824 [27.3%] had depressive symptoms; 1668 [55.8%] had amyloid pathology), the presence of depressive symptoms was associated with a lower likelihood of amyloid pathology (OR, 0.73; 95% CI 0.61–0.89; $P = .001$). When considering subgroup effects, in individuals with NC, the presence of depressive symptoms was associated with a higher frequency of amyloid pathology in APOE 4 noncarriers (mean difference, 5.0%; 95% CI 1.0–9.0; $P = .02$) but not in APOE 4 carriers. This was not the case in individuals with MCI.

Conclusions and relevance: Depressive symptoms were not consistently associated with a higher frequency of amyloid pathology in participants with NC and were associated with a lower likelihood of amyloid pathology in participants with MCI. These findings were not influenced by age, sex, or education level. Mechanisms other than amyloid accumulation may commonly underlie depressive symptoms in late life.

- DE WITTE, S., DE RAEDT, R., WU, G. R., DE SMET, S., DEDONCKER, J., KLOOSTER, D., TANDT, H., VAN DE VELDE, N., DE SCHRIJVER, N., HERREMANS, S., DEBRUYCKERE, I., NOBELS, A., KOSTER, E. H. W., LEMMENS, G., VANDERHASSELT, M. A., & **BAEKEN, C.**

Assessing accelerated iTBS in treatment-resistant depression: Doubling the number of pulses per session does not double the response rates.

Brain Stimul. 2025 Mar-Apr;18(2):195–197. doi: 10.1016/j.brs.2025.02.004.

Background: Accelerated intermittent theta burst stimulation (aiTBS) offers rapid antidepressant effects for treatment-resistant depression (TRD). Yet, dose response relationships (number of sessions and number of pulses per session) are not fully understood. Objectives: This first phase of our Stepped-Care aiTBS 2 Depression double-blind randomized controlled trial (NCT03288675) aims to assess whether the increased pulse count enhances reductions in depressive symptoms, suicidal ideation, anxiety, psychomotor disturbances, and hopelessness among patients with TRD.

Methods: We extended our previous aiTBS research by increasing the pulse count per session from 1,620 to 3,000 pulses—nearly doubling it—while keeping all other clinical and stimulation parameters unchanged from our earlier trial (NCT01832805). Sixty-eight TRD patients, all of the melancholic subtype, received 20 either active or sham aiTBS sessions over four days, targeting the left dorsolateral prefrontal cortex. Primary outcomes were assessed through changes in clinician-rated depressive symptoms.

Results: Although active treatment demonstrated higher response (12.50%) and remission rates (6.25%) than sham (8.82% response; 0.00% remission), these rates were unexpectedly lower than those observed in our previous comparable studies using nearly half the number of pulses per session. We found no significant differential effect of active or sham stimulation on suicidal ideation, hopelessness, psychomotor disturbances, or anxiety.

Conclusion: Increasing the pulse count per session in aiTBS treatment does not significantly improve clinical outcomes in melancholic TRD, indicating that there is no linear association with increasing the number of pulses per session and clinical outcome rates.

Acknowledgments

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Foundation for Neurosciences and by an Applied Biomedical (TBM) grant of the Agency for Innovation through Science and Technology (IWT), part of the Research Foundation - Flanders (FWO) PrevenD Project 2.0 (T000720N), the BRAINN HORIZON-WIDERA-2021-ACCESS-03 – Twinning project Grant No.: 101079001, and a BOF16/GOA/017 grant for a Concerted Research Action of Ghent University (R.D.R., E.K., & C.B). MAV received funding from FWO-Flanders for research projects for fundamental research (Grant Numbers: G044222N; G044019N). RDR and MAV are supported by a grant for a Concerted Research Action of the Special Research Fund of Ghent University (01G00623). SDS is funded by a FWO-Flanders PhD fellowship (Grant Number: 3F001120).

- VAN ROSSEM, D., ALLEMEERSCH, G.-J., BARROS, N., TEMMERMAN, J., DESMET, M., RINGOOT, I., RIBBENS, A., MICHIELS, V., DE MEY, J., BAEKEN, C., **ENGELBORGH, S.**, & DE WITTE, S. (2025).

Assessing the link between cerebellar volume and cognitive function in Alzheimer's disease: a pilot study.

Scientific Reports - Nature, 15(1), 1-12. Artikel 32943. <https://doi.org/10.1038/s41598-025-12975-8>, <https://doi.org/10.1038/s41598-025-12975-8>, <https://doi.org/10.1038/s41598-025-12975-8>

Background: Neurodegenerative diseases, such as Alzheimer's disease (AD), are characterized by pathological changes in the brain including specific patterns of brain atrophy. These atrophy patterns often mirror intrinsic connectivity networks linked to cognition, such as the default mode network. While research has focused on the changes in the cortex, emerging evidence highlights similar alterations in the cerebellum. Traditionally linked to motor functions, the cerebellum is now recognized for its role in (social) cognition.

Hypothesis and objectives: We hypothesize that individuals within the AD continuum will exhibit significant reductions in grey matter volume, particularly in the posterior cerebellar lobule VII especially Crus I/II, with more pronounced reductions in the later stages of AD. We also expect that cerebellar atrophy will be linked to cognitive performance. This study investigates the relationship between differences in cerebellar volume and cognitive function across the AD continuum.

Materials and methods: Subjects with subjective cognitive decline (SCD, n = 45), mild cognitive impairment due to AD (MCI, n = 23), and dementia due to AD (ADD, n = 62) were selected from an existing memory-clinic based research database. A comprehensive neuropsychological assessment conducted as part of the diagnostic process was available for all participants. The Mini-Mental State Examination (MMSE) and the Addenbrooke's Cognitive Examination-Revised (ACE-R) were selected for this study as an indication of cognitive performance. Brain magnetic resonance imaging (MRI) scans were processed using the automated brain volumetry software icobrain dm. For this pilot study, the cerebellar segmentations from icobrain were combined with an atlas-based approach to obtain a finer anatomical parcellation of the cerebellum. Finally, the volume for different cerebellar regions was determined, including the entire cerebellum (both grey and white matter), as well as grey matter of the left and right anterior cerebellum (lobules I-IV), posterior cerebellum (lobules VI-IX, with lobule VII being subdivided into VIIa with Crus I/II, VIIb), and the flocculonodular lobe (lobule X).

Results: Our results identified significant volumetric differences in 14 cerebellar regions between the SCD and ADD groups, including lobule VII/Crus II. Notably, no differences in volume were found in the MCI group as compared to the ADD group. Further analysis demonstrated that cognitive performance (measured by the MMSE and ACE-R) positively correlated with grey matter volume in various regions of the posterior cerebellum for both the MCI and ADD groups. However, no correlations between brain volume and cognitive performance were observed in the SCD group.

Conclusions: These findings support the hypothesis that cerebellar atrophy is associated with cognitive symptoms of neurodegenerative diseases like AD. Understanding this association could provide new insights into the pathophysiology of AD symptoms and possibly pave the way to targeted neuromodulator therapeutic strategies.

Acknowledgments

This work was supported by the Geneeskundige Stichting Koningin Elisabeth / Fondation Médicale Reine Elisabeth (GSKE).

- ZHANG, Y., WU, G., DE WITTE, S., & BAEKEN, C. (2025).

Microstructural alterations in superficial white matter associated with anhedonia and suicidal ideation in major depressive disorder.

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 10(–), 1–13.
<https://doi.org/10.1016/j.bpsc.2025.02.010>

Background: Major depressive disorder (MDD) is characterized by disturbances in emotional and cognitive functioning, including anhedonia and suicidal ideation. Neuroimaging research has traditionally focused on deep white matter (DWM) tracts connecting distant brain regions. However, superficial white matter (SWM)—consisting of short-range fibers connecting adjacent cortical areas—accounts for the majority of cortico-cortical connections and may play a critical role in integrating gray and white matter alterations. Despite its relevance, SWM abnormalities in MDD remain understudied.

Hypothesis and objectives: The authors hypothesized that patients with MDD would show significant microstructural abnormalities in SWM compared with healthy controls (HCs). They further expected that these SWM alterations would be associated with core depressive symptoms, particularly anhedonia and suicidal ideation. Finally, the study aimed to determine whether neurite orientation dispersion and density imaging (NODDI) metrics would provide more specific information on SWM pathology than conventional diffusion tensor imaging (DTI) metrics.

Materials and methods: The study included 62 antidepressant-free patients with melancholic, treatment-resistant MDD and 77 healthy controls aged 18–65 years. All participants underwent diffusion-weighted MRI on a 3T scanner. SWM bundles were reconstructed using probabilistic tractography seeded from the gray–white matter interface. Microstructural properties were assessed using DTI metrics (fractional anisotropy [FA], mean diffusivity [MD]) and NODDI metrics (neurite density index [NDI], orientation dispersion index [ODI]). Voxelwise tract-based spatial statistics restricted to SWM were used for group comparisons, controlling for age and sex. Correlations between diffusion metrics and clinical measures—including anhedonia (SHAPS) and suicidal ideation (SSI)—were examined with correction for multiple comparisons.

Results: Compared with healthy controls, patients with MDD showed widespread SWM abnormalities. DTI analyses revealed reduced FA and increased MD in SWM bundles connecting frontal, temporal, parietal, and occipital cortices. NODDI analyses demonstrated reduced NDI in SWM bundles connecting frontal–parietal–temporal regions and increased ODI in parietal, occipital, and posterior cingulate connections. Crucially, reduced neurite density in SWM bundles connecting prefrontal cortex and insula was significantly negatively correlated with anhedonia and suicidal ideation in the MDD group, but not in healthy controls.

Conclusions: This study provides evidence that superficial white matter microstructure is significantly altered in major depressive disorder and is closely linked to clinically relevant symptoms. Reduced neurite density in prefrontal–insula SWM connections may constitute a structural substrate for anhedonia and suicidal ideation. Furthermore, NODDI metrics appear more specific than conventional DTI measures in detecting SWM abnormalities. These findings highlight SWM as a critical but previously underrecognized component of the neurobiology of

MDD and suggest potential targets for neuromodulatory interventions.

Acknowledgments and Disclosures

This work was supported by the National Natural Science Foundation of China (Grant Nos. 62271415 and 61876156 [to GW]). CB is supported by the **Queen Elisabeth Medical Foundation for Neurosciences**; by an Applied Biomedical (TBM) grant of the Agency for Innovation through Science and Technology (IWT), part of the Research Foundation—Flanders (FWO) PrevenD Project 2.0 (Grant No. T000720N); by the BRAINN HORIZON-WIDERA-2021-ACCESS-03—Twinning project (Grant No. 101079001); and by the SAO-FRA 2024-0023. YZ is supported by fellowship funding from the China Scholarship Council (Grant No. 202106750013).



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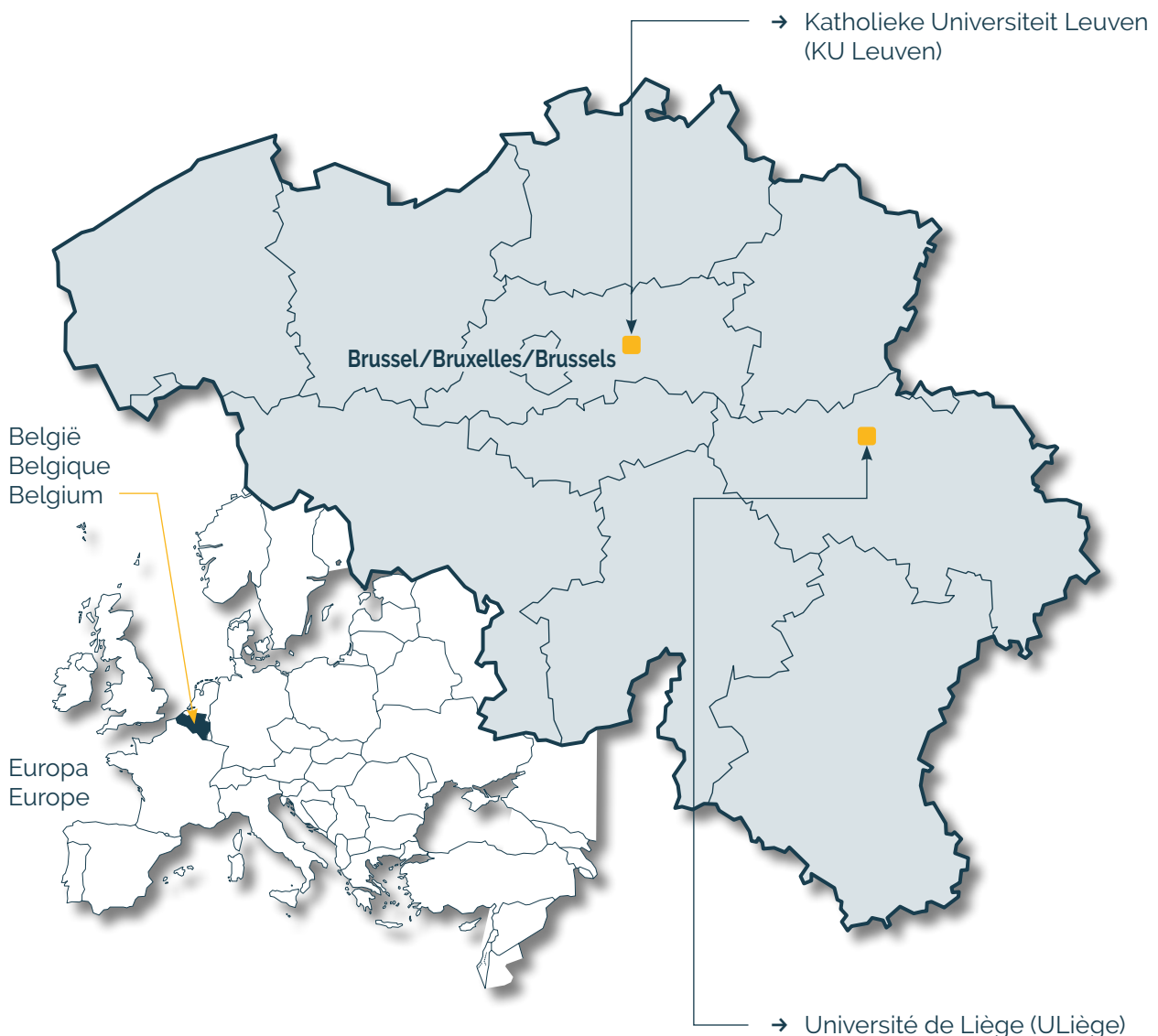
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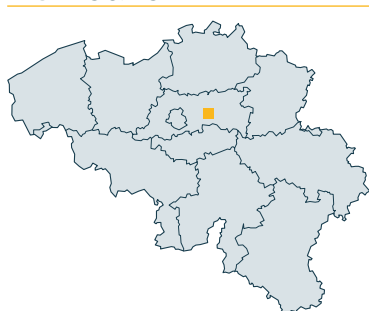


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KU Leuven



Prof. dr. Bart De Strooper (VIB)

A vicious A β oligomers-dependent neuron-microglia cycle fuels Alzheimer's Disease

Prof. dr. Pierre Vanderhaeghen (VIB)

Deciphering the mechanisms underlying neurogenesis defects in mitochondrial diseases

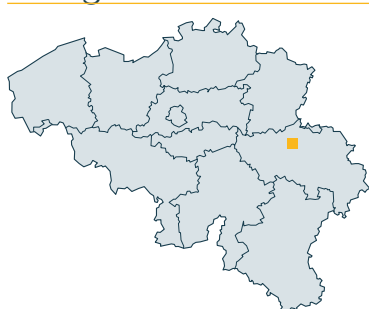
Prof. dr. Veerle Baekelandt

The role of LRRK2 in the peripheral immune system and gut-to-brain spreading of alpha-synuclein pathology in Parkinson's disease

Prof. dr. Thomas Voets

Unraveling the etiology of TRPM3-dependent neurodevelopmental disorders

ULiège



Prof. dr. Pierre Maquet

Quantitative MRI at 7 Tesla addresses ten questions about brain small vessel diseases



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KU Leuven

Prof. dr. Bart de Strooper (KU Leuven)

VIB Center for Brain and Disease Research

Herestraat 49

3000 Leuven

Belgium

T +32 495 77 10 44

Bart.Destrooper@vib.be

Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

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MEG3 activates necroptosis in human neuron xenografts modeling Alzheimer's disease.

Science (New York, N.Y.), 381(6663), 1176–1182. <https://doi.org/10.1126/science.abp9556> –

Abstract

Neuronal cell loss is a defining feature of Alzheimer's disease (AD), but the underlying mechanisms remain unclear. We xenografted human or mouse neurons into the brain of a mouse model of AD. Only human neurons displayed tangles, Gallyas silver staining, granulovacuolar neurodegeneration (GVD), phosphorylated tau blood biomarkers, and considerable neuronal cell loss. The long noncoding RNA *MEG3* was strongly up-regulated in human neurons. This neuron-specific long noncoding RNA is also up-regulated in AD patients. *MEG3* expression alone was sufficient to induce necroptosis in human neurons *in vitro*. Down-regulation of *MEG3* and inhibition of necroptosis using pharmacological or genetic manipulation of receptor-interacting protein kinase 1 (RIPK1), RIPK3, or mixed lineage kinase domain-like protein (MLKL) rescued neuronal cell loss in xenografted human neurons. This model suggests potential therapeutic approaches for AD and reveals a human-specific vulnerability to AD.

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Abstract

The clinical definition of neurodegenerative diseases is based on symptoms that reflect terminal damage of specific brain regions. This is misleading as it tells little about the initial disease processes. Circuitry failures that underlie the clinical symptomatology are themselves preceded by clinically mostly silent, slowly progressing multicellular processes that trigger or are triggered by the accumulation of abnormally folded proteins such as A, Tau, TDP-43, and α -synuclein, among others. Methodological advances in single-cell omics, combined with complex genetics and novel ways to model complex cellular interactions using induced pluripotent stem (iPS) cells, make it possible to analyze the early cellular phase of neurodegenerative disorders. This will revolutionize the way we study those diseases and will translate into novel diagnostics and cell-specific therapeutic targets, stopping these disorders in their early track before they cause difficult-to-reverse damage to the brain.

Keywords: Alzheimer's disease; Parkinson's disease; neurodegeneration; single-cell sequencing.

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Early alterations in the MCH system link aberrant neuronal activity and sleep disturbances in a mouse model of Alzheimer's disease.

Nature Neuroscience, 26(6), 1021–1031. <https://doi.org/10.1038/s41593-023-01325-4> –

- Abstract

Early Alzheimer's disease (AD) is associated with hippocampal hyperactivity and decreased sleep quality. Here we show that homeostatic mechanisms transiently counteract the increased excitatory drive to CA1 neurons in App^{NL-G-F} mice, but that this mechanism fails in older mice. Spatial transcriptomics analysis identifies Pmch as part of the adaptive response in App^{NL-G-F} mice. Pmch encodes melanin-concentrating hormone (MCH), which is produced in sleep-active lateral hypothalamic neurons that project to CA1 and modulate memory. We show that MCH downregulates synaptic transmission, modulates firing rate homeostasis in hippocampal neurons and reverses the increased excitatory drive to CA1 neurons in App^{NL-G-F} mice. App^{NL-G-F} mice spend less time in rapid eye movement (REM) sleep. App^{NL-G-F} mice and individuals with AD show progressive changes in morphology of CA1-projecting MCH axons. Our findings identify the MCH system as vulnerable in early AD and suggest that impaired MCH-system function contributes to aberrant excitatory drive and sleep defects, which can compromise hippocampus-dependent functions.

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The γ -secretase substrate proteome and its role in cell signaling regulation.

Molecular Cell, 83(22), 4106-4122.e10.

<https://doi.org/10.1016/j.molcel.2023.10.029>

-

Abstract

Protein phosphorylation is an important cellular regulatory mechanism as many enzymes and receptors are activated/deactivated by phosphorylation and dephosphorylation events, by means of kinases and phosphatases. In particular, the protein kinases are responsible for cellular transduction signaling and their hyperactivity, malfunction or overexpression can be found in several diseases, mostly tumors. Therefore, it is evident that the use of kinase inhibitors can be valuable for the treatment of cancer. In this review, we discuss the mechanism of action of phosphorylation, with particular attention to the importance of phosphorylation under physiological and pathological conditions. We also discuss the possibility of using kinase

inhibitors in the treatment of tumors.

Keywords: protein phosphorylation, kinase, phosphatase, phospho-signaling networks, cancer, drug target

Acknowledgments

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- RUÉ, L., JASPERS, T., DEGORS, I. M. S., NIPPEN, S., SCHOLS, D., DE STROOPER, B., & DEWILDE, M. (2023).

Novel Human/NonHuman Primate Cross-Reactive Anti-Transferrin Receptor Nanobodies for Brain Delivery of Biologics.

Pharmaceutics, 15(6). <https://doi.org/10.3390/pharmaceutics15061748> –

Abstract

The blood-brain barrier (BBB), while being the gatekeeper of the central nervous system (CNS), is a bottleneck for the treatment of neurological diseases. Unfortunately, most of the biologicals do not reach their brain targets in sufficient quantities. The antibody targeting of receptor-mediated transcytosis (RMT) receptors is an exploited mechanism that increases brain permeability. We previously discovered an anti-human transferrin receptor (TfR) nanobody that could efficiently deliver a therapeutic moiety across the BBB. Despite the high homology between human and cynomolgus TfR, the nanobody was unable to bind the non-human primate receptor. Here we report the discovery of two nanobodies that were able to bind human and cynomolgus TfR, making these nanobodies more clinically relevant. Whereas nanobody BBB00515 bound cynomolgus TfR with 18 times more affinity than it did human TfR, nanobody BBB00533 bound human and cynomolgus TfR with similar affinities. When fused with an anti-beta-site amyloid precursor protein cleaving enzyme (BACE1) antibody (1A11AM), each of the nanobodies was able to increase its brain permeability after peripheral injection. A 40% reduction of brain A₁₋₄₀ levels could be observed in mice injected with anti-TfR/BACE1 bispecific antibodies when compared to vehicle-injected mice. In summary, we found two nanobodies that could bind both human and cynomolgus TfR with the potential to be used

clinically to increase the brain permeability of therapeutic biologicals.

Keywords: nanobody, VHH, transferrin receptor, blood-brain barrier, receptor-mediated transcytosis

Funding

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- SERNEELS, L., NARLAWAR, R., PEREZ-BENITO, L., MUNICOY, M., GUALLAR, V., T'SYEN, D., DEWILDE, M., BISCHOFF, F., FRAIPONTS, E., TRESADERN, G., ROEVENS, P. W. M., GIJSEN, H. J. M., & DE STROOPER, B. (2023).

Selective inhibitors of the PSEN1-gammasecretase complex.

The Journal of Biological Chemistry, 299(6), 104794. <https://doi.org/10.1016/j.jbc.2023.104794> –

Abstract

Clinical development of γ -secretases, a family of intramembrane cleaving proteases, as therapeutic targets for a variety of disorders including cancer and Alzheimer's disease was aborted because of serious mechanism-based side effects in the phase III trials of unselective inhibitors. Selective inhibition of specific γ -secretase complexes, containing either PSEN1 or PSEN2 as the catalytic subunit and APH1A or APH1B as supporting subunits, does provide a feasible therapeutic window in preclinical models of these disorders. We explore here the pharmacophoric features required for PSEN1 *versus* PSEN2 selective inhibition. We synthesized a series of brain penetrant 2-azabicyclo[2.2.2]octane sulfonamides and identified a compound with low nanomolar potency and high selectivity (>250-fold) toward the PSEN1-APH1B subcomplex *versus* PSEN2 subcomplexes. We used modeling and site-directed mutagenesis to identify critical amino acids along the entry part of this inhibitor into the catalytic site of PSEN1. Specific targeting one of the different γ -secretase complexes might provide safer drugs in the future.

Keywords: γ -secretase, inhibitors, selectivity, therapy, medicinal chemistry

Acknowledgments

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Publications in 2024 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- BALIGÁCS N, ALBERTINI G, BORRIE SC, SERNEELS L, PRIDANS C, BALUSU S, DE STROOPER B.

Homeostatic microglia initially seed and activated microglia later reshape amyloid plaques in Alzheimer's Disease.

Nat Commun. 2024 Dec 5;15(1):10634. doi: 10.1038/s41467-024-54779-w.

PMID: 39639016; PMCID: PMC11621353. IF: 16.6; Q1

Abstract

The role of microglia in the amyloid cascade of Alzheimer's disease (AD) is debated due to conflicting findings. Using a genetic and a pharmacological approach we demonstrate that depletion of microglia before amyloid- β (A β) plaque deposition, leads to a reduction in plaque numbers and neuritic dystrophy, confirming their role in plaque initiation. Transplanting human microglia restores A β plaque formation. While microglia depletion reduces insoluble A β levels, soluble A β concentrations stay consistent, challenging the view that microglia clear A β . In later stages, microglial depletion decreases plaque compaction and increases neuritic dystrophy, suggesting a protective role. Human microglia with the TREM2R47H/R47H mutation exacerbate plaque pathology, emphasizing the importance of non-reactive microglia in the initiation of the amyloid cascade. Adaptive immune depletion (Rag2-/-) does not affect microglia's impact on plaque formation. These findings clarify conflicting reports, identifying microglia as key drivers of amyloid pathology, and raise questions about optimal therapeutic strategies for AD

Acknowledgments

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- DE STROOPER B, HAASS C, HARDY J, ZETTERBERG H.

Divisions over the regulation of lecanemab.

Lancet. 2024 Nov 30;404(10468):2160-2161. doi: 10.1016/S0140-6736(24)02513-3. Epub 2024 Nov 14. PMID: 39551058. IF: 98.4; Q1 (but is only a letter)

- PREMAN P, MOECHARS D, FERTAN E, WOLFS L, SERNEELS L, SHAH D, LAMOTE J, POOVATHINGAL S, SNELLINX A, MANCUSO R, BALUSU S, KLENERMAN D, ARRANZ AM, FIERIS M, DE STROOPER B.

APOE from astrocytes restores Alzheimer's A-pathology and DAM-like responses in APOE deficient microglia.

EMBO Mol Med. 2024 Dec;16(12):3113-3141. doi: 10.1038/s44321-024-00162-7. Epub 2024 Nov 11. PMID: 39528861; PMCID: PMC11628604. IF 9.0 Q1

Abstract

The major genetic risk factor for Alzheimer's disease (AD), APOE4, accelerates beta-amyloid (A β) plaque formation, but whether this is caused by APOE expressed in microglia or astrocytes is debated. We express here the human APOE isoforms in astrocytes in an Apoe-deficient AD mouse model. This is not only sufficient to restore the amyloid plaque pathology but also induces the characteristic transcriptional pathological responses in Apoe-deficient microglia surrounding the plaques. We find that both APOE4 and the protective APOE2 from astrocytes increase fibrillar plaque deposition, but differentially affect soluble A β aggregates. Microglia and astrocytes show specific alterations in function of APOE genotype expressed in astrocytes. Our experiments indicate a central role of the astrocytes in APOE mediated amyloid plaque pathology and in the induction of associated microglia responses. Keywords Alzheimer's Disease; Astrocytes; Microglia; APOE; β -amyloid Pathology

Acknowledgments

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- KOPER MJ, MOONEN S, RONISZ A, OSPITALIERI S, CALLAERTS-VEGH Z, T'SYEN D, RABE S, STAUFENBIEL M, DE STROOPER B, BALUSU S, THAL DR.

Inhibition of an Alzheimer's disease-associated form of necroptosis rescues neuronal death in mouse models.

Sci Transl Med. 2024 Oct 30;16(771):eadf5128. doi: 10.1126/scitranslmed.adf5128. Epub 2024 Oct 30. PMID: 39475569. IF 15.8, Q1

Abstract

Necroptosis is a regulated form of cell death that has been observed in Alzheimer's disease (AD) along with the classical pathological hallmark lesions of amyloid plaques and Tau neurofibrillary tangles. To understand the neurodegenerative process in AD, we studied the role of necroptosis in mouse models and primary mouse neurons. Using immunohistochemistry, we demonstrated activated necroptosis-related proteins in transgenic mice developing Tau pathology and in primary neurons from amyloid precursor protein (APP)-Tau double transgenic mice treated with phosphorylated Tau seeds derived from a patient with AD but not in APP transgenic mice that only exhibited β -amyloid deposits. Necroptosis proteins in granulovacuolar degeneration (GVD) bodies were associated with neuronal loss in mouse brain regions also known to be vulnerable to GVD in the human AD brain. Necroptosis inhibitors lowered the percentage of neurons showing GVD and reduced neuronal loss, both in transgenic mice and in primary mouse neurons. This suggests that a GVD-associated form of necroptosis that we refer to as "GVD-necroptosis" may represent a delayed form of necroptosis in AD. We propose that inhibition of necroptosis could rescue this type of neuronal death in AD.

- BALUSU S, DE STROOPER B.

The necroptosis cell death pathway drives neurodegeneration in Alzheimer's disease.

Acta Neuropathol. 2024 Jun 9;147(1):96. doi: 10.1007/s00401-024-02747-5. - PMID: 38852117; PMCID: PMC11162975. IF 13.1, Q1

Abstract

Although apoptosis, pyroptosis, and ferroptosis have been implicated in AD, none fully explains the extensive neuronal loss observed in AD brains. Recent evidence shows that necroptosis is abundant in AD, that necroptosis is closely linked to the appearance of Tau pathology, and that necroptosis markers accumulate in granulovacuolar neurodegeneration vesicles (GVD). We review here the neuron-specific activation of the granulovacuolar mediated neuronal-necroptosis pathway, the potential AD-relevant triggers upstream of this pathway, and the interaction of the necrosome with the endo-lysosomal pathway, possibly providing links to Tau pathology. In addition, we underscore the therapeutic potential of inhibiting necroptosis in neurodegenerative diseases such as AD, as this presents a novel avenue for drug development targeting neuronal loss to preserve cognitive abilities. Such an approach seems particularly relevant when combined with amyloid-lowering drugs.

Acknowledgments

Figures 2 and 3 were generated using Biorender. BDS laboratory is supported by a European Research Council (ERC) grant CELLPHASE_AD834682 (EU), FWO, KU Leuven, VIB, Stichting Alzheimer Onderzoek, Belgium (SAO), the UCB grant from the Elisabeth Foundation, a Methusalem grant from KU Leuven and the Flemish Government. BDS is also supported by the UK Dementia Research Institute through UK DRI Ltd, principally funded by the Medical Research Council (grant no. MR/Y014847/1). B.D.S. is the Bax-Vanlufelen Chair for Alzheimer's disease and is supported by the Opening the Future campaign and Mission Lucidity of KUL, Leuven University. SB is a Fonds voor Wetenschappelijk Onderzoek—Vlaanderen (FWO) senior

postdoctoral scholar (12P5922N). We particularly thank CureALZ for funding our ongoing necroptosis work.

- MANCUSO R, FATTORELLI N, MARTINEZ-MURIANA A, DAVIS E, WOLFS L, VAN DEN DAELE J, GERIC I, PREMEREUR J, POLANCO P, BIJNENS B, PREMAN P, SERNEELS L, POOVATHINGAL S, BALUSU S, VERFAILLIE C, FIERIS M, DE STROOPER B.

Xenografted human microglia display diverse transcriptomic states in response to Alzheimer's disease-related amyloid- β pathology

Nat Neurosci. 2024 May;27(5):886-900. doi: 10.1038/s41593-024-01600-y. Epub 2024 Mar 27. PMID: 38539015; PMCID: PMC11089003. IF: 21.2, Q1

Abstract

Microglia are central players in Alzheimer's disease pathology but analyzing microglial states in human brain samples is challenging due to genetic diversity, postmortem delay and admixture of pathologies. To circumvent these issues, here we generated 138,577 single-cell expression profiles of human stem cell-derived microglia xenotransplanted in the brain of the AppNL-G-F model of amyloid pathology and wild-type controls. Xenografted human microglia adopt a disease-associated profile similar to that seen in mouse microglia, but display a more pronounced human leukocyte antigen or HLA state, likely related to antigen presentation in response to amyloid plaques. The human microglial response also involves a pro-inflammatory cytokine/chemokine response microglia or CRM response to oligomeric A β oligomers. Genetic deletion of TREM2 or APOE as well as APOE polymorphisms and TREM2R47H expression in the transplanted microglia modulate these responses differentially. The expression of other Alzheimer's disease risk genes is differentially regulated across the distinct cell states elicited in response to amyloid pathology. Thus, we have identified multiple transcriptomic cell states adopted by human microglia in a multipronged response to Alzheimer's disease-related pathology, which should be taken into account in translational studies.

Acknowledgments

This project received funding from the European Research Council (ERC) under the European Union's Horizon 2020 Research and Innovation Programme (grant agreement no. ERC-834682 CELLPHASE_AD). This work was also supported by UKRI-MRC (grant no. MR/Y014847/1), the UK Dementia Research Institute, the Flanders Institute for Biotechnology (VIB vzw), a Methusalem grant from KU Leuven and the Flemish Government, the Fonds voor Wetenschappelijk Onderzoek, KU Leuven, the Queen Elisabeth Medical Foundation for Neurosciences, the Opening the Future campaign of the Leuven Universitair Fonds, the Belgian Alzheimer Research Foundation (SAO-FRA) and the Alzheimer's Association USA. R.M. has funding from the ERC under the European Union's Horizon 2020 Research and Innovation Programme (project no. 101041867—XenoMicrogliaAD) and Fonds voor Wetenschappelijk Onderzoek (grants no. GoC9219N, Go56022N and GoK9422N), and is a recipient of a postdoctoral fellowship from the Alzheimer's Association USA (fellowship nos. 2018-AARF-591110 and 2018-AARF-591110-RAPID). He also receives funding from BrightFocus Foundation (grant no. A2021034S), SAO-FRA (grant no. 2021/0021) and the University of Antwerp (grant no. BOF-TOP 2022-2025). B.D.S. holds the Bax-Vanlufelen Chair for Alzheimer's Disease. N.F. is the recipient of a PhD fellowship from Fonds voor Wetenschappelijk Onderzoek (fellowship no. 1139520N). A.M.-M. is supported by a fellowship from the Alzheimer's Association USA (fellowship no. AARF-20-684397) and an FWO-Marie Skłodowska-Curie Actions—Seal of Excellence Postdoctoral Fellowship (fellowship no. 12ZX621N). C.V. receives funding from Fonds voor Wetenschappelijk Onderzoek (grants no. GoB5819 and So01221N). J.P. is the recipient of a PhD fellowship from Fonds voor Wetenschappelijk Onderzoek (fellowship no. 1122423N). B.B. is the recipient of a PhD fellowship from the University of Antwerp (DOCPRO fellowship no. FFB210307).

Publications in 2025 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- GIULIA ALBERTINI· MAGDALENA ZIELONKA· MARIE-LYNN CUYPERS· AN SNELLINX· CIANA XU³, SURESH POOVATHINGAL· MARTA WOJNO· KRISTOFER DAVIE· VEERLE VAN LIESHOUT, KATLEEN CRAESSAERTS· LEEN WOLFS· EMANUELA PASCIUTO· TOM JASPERS· KATRIEN HORRÉ· LURGARDE SERNEELS· MARK FIERS· MAARTEN DEWILDE· **BART DE STROOPER**

Affiliations Expand

The Alzheimer's therapeutic Lecanemab attenuates A pathology by inducing an amyloid-clearing program in microglia

Nat Neurosci 026 Jan;29(1):100-110. doi: 10.1038/s41593-025-02125-8. Epub 2025

PMCID: PMC12779577 DOI: 10.1038/s41593-025-02125-8

Abstract

Controversies over anti-amyloid immunotherapies underscore the need to elucidate their mechanisms of action. Here we demonstrate that Lecanemab, a leading anti-amyloid (A) antibody, mediates amyloid clearance by activating microglial effector functions. Using a human microglia xenograft mouse model, we show that Lecanemab significantly reduces A pathology and associated neuritic damage, while neither fragment crystallizable (Fc)-silenced Lecanemab nor microglia deficiency elicits this effect despite intact plaque binding. Single-cell RNA sequencing and spatial transcriptomic analyses reveal that Lecanemab induces a focused transcriptional program that enhances phagocytosis, lysosomal degradation, metabolic reprogramming, interferon genes and antigen presentation. Finally, we identify SPP1/osteopontin as a major factor induced by Lecanemab treatment and demonstrate its role in promoting A clearance. These findings highlight that effective amyloid removal depends on the engagement of microglia through the Fc fragment, providing critical insights for optimizing anti-amyloid therapies in Alzheimer's disease.

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and maintained at the University of Iowa, Department of Biology.

Review

- D JAKABEK, A M ISAACS, **B DE STROOPER**, M TUSZYNSKI, R LANE, O USPENSKAYA, E MCDADE, M S RAFII, C J MUMMERY

CTAD taskforce: genetic therapies in Alzheimer's disease

J Prev Alzheimers Dis 2025 Sep;12(8):100269. doi: 10.1016/j.tjpad.2025.100269. Epub 2025 Jul 9. Affiliations Expand

PMID: 40634156 - PMCID: PMC12413703 - DOI: 10.1016/j.tjpad.2025.100269

Abstract

There are an increasing number of genetic approaches to treating Alzheimer's disease and other dementias, with some promising results from early-phase trials. This prompted the convention of the first EU-US CTAD Task Force on genetic therapies in Alzheimer's disease in October 2024. Preclinical studies and clinical trials of genetic therapies in Alzheimer's disease and other dementias are presented here with key lessons for the field. Importantly, there are several challenges and opportunities unique to neurogenetic therapies which were reviewed and discussed, including means of genetic manipulation, adverse events, monitoring, timing of therapy, and the importance of patient involvement in trial design. Continued collaboration across disciplines will accelerate development of neurogenetic therapeutics.

Keywords: AAV; ASO; Genetic therapy; RCTs; siRNA.

- KITTY B. MURPHY, DI HU, LEEN WOLFS, SUSAN K. ROHDE, GONZALO LEGUÍA FAURÓ, IVANA GERIC, RENZO MANCUSO, BART DE STROOPER & SARAH J. MARZI

The APOE isoforms differentially shape the transcriptomic and epigenomic landscapes of human microglia xenografted into a mouse model of Alzheimer's disease

Nature Communications volume 16, Article number: 4883 (2025)

Abstract

Microglia play a key role in the response to amyloid beta in Alzheimer's disease (AD). In this context, the major transcriptional response of microglia is the upregulation of *APOE*, the strongest late-onset AD risk gene. Of its three isoforms, *APOE2* is thought to be protective, while *APOE4* increases AD risk. We hypothesised that the isoforms change gene regulatory patterns that link back to biological function by shaping microglial transcriptomic and chromatin landscapes. We use RNA- and ATAC-sequencing to profile gene expression and chromatin accessibility of human microglia xenotransplanted into the brains of male APP^{NL-G-F} mice. We identify widespread transcriptomic and epigenomic differences which are dependent on *APOE* genotype and are corroborated across the profiling assays. Our results indicate that impaired microglial proliferation, migration and immune responses may contribute to the increased risk for late-onset AD in *APOE4* carriers, while increased phagocytic capabilities and DNA-binding of the vitamin D receptor in *APOE2* microglia may contribute to the isoform's protective role.

Acknowledgments

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(ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No. 834682 CELLPHASE_AD). RM has funding from the European Research Council (ERC) under the European Union's Horizon 2020 Research and Innovation Programme (project no. 101041867—XenoMicrogliaAD), Fonds voor Wetenschappelijk Onderzoek (grants no. GoC9219N, Go56022N and GoK9422N) and is a recipient of a postdoctoral fellowship from the Alzheimer's Association USA (fellowship no. 2018-AARF-591110 and 2018-AARF-591110-RAPID). He also receives funding from the Alzheimer's Association (E2A-23-1148152, 23AARF-1026404 and ABA-22-968700), BrightFocus Foundation (A2021034S), SAO-FRA (grant no. 2021/0021) and the University of Antwerp (BOF-TOP 2022-2025). KBM is a recipient of an MRC Doctoral Training Partnership award. We thank Annerieke Sierksma for helpful discussions and feedback. We thank the members of the International Neuroimmune Consortium for their insightful conversations and support in this project. The Imperial BRC Genomics Facility has provided resources and support that have contributed to the research results reported within this paper. The Imperial BRC Genomics Facility is supported by NIHR funding to the Imperial Biomedical Research Centre and **the Queen Elisabeth Medical Foundation for Neurosciences**

- **BART DE STROOPER**, PHILIP SCHELTENS, STEPHEN SALLOWAY

Editorial: Breaking Barriers: Delivering Therapeutics to the Brain in Alzheimer's Disease

J Prev Alzheimers Dis 2025 Jun 13;12(7):100229. doi: 10.1016/j.tjpad.2025.100229

PMCID: PMC12321621 PMID: 40517082

- LUTGARDE SERNEELS· ANNERIEKE SIERKSMA· EMANUELA PASCIUTO· IVANA GERIC· ARYA NAIR· ANNA MARTINEZ-MURIANA· AN SNEELINX· **BART DE STROOPER**

A versatile mouse model to advance human microglia transplantation research in neurodegenerative diseases

Mol Neurodegener 2025 Mar 11;20(1):29. doi: 10.1186/s13024-025-00823-2.

Affiliations Expand

PMID: 40069774 - PMCID: PMC11895352 - DOI: 10.1186/s13024-025-00823-2

Abstract

Background: Recent studies highlight the critical role of microglia in neurodegenerative disorders, and emphasize the need for humanized models to accurately study microglial responses. Human-mouse microglia xenotransplantation models are a valuable platform for functional studies and for testing therapeutic approaches, yet currently those models are only available for academic research. This hampers their implementation for the development and testing of medication that targets human microglia.

Methods: We developed the hCSF1^{Bdes} mouse line, which is suitable as a new transplantation model and available to be crossed to any disease model of interest. The hCSF1^{Bdes} model created by CRISPR gene editing is RAG2 deficient and expresses human CSF1. Additionally, we crossed this model with two humanized App KI mice, the App^{Hu} and the App^{SAA}. Flow cytometry, immunohistochemistry and bulk sequencing was used to study the response of microglia in the context of Alzheimer's disease.

Results: Our results demonstrate the successful transplantation of iPSC-derived human microglia into the brains of hCSF1^{Bdes} mice without triggering a NK-driven immune response. Furthermore, we confirmed the multipronged response of microglia in the context of Alzheimer's disease. The hCSF1^{Bdes} and the crosses with the Alzheimer's disease knock-in model App^{SAA} and the humanized App knock-in control mice, App^{Hu} are deposited with EMMA and fully accessible to the research community.

Conclusion: The hCSF1^{Bdes} mouse is available for both non-profit and for-profit organisations, facilitating the use of the xenotransplantation paradigm for human microglia to study complex

human disease.

Keywords: Alzheimer's disease; Microglia; Mouse xenotransplantation model.

Acknowledgments

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Prof. Pierre Vanderhaeghen, MD, PhD

Stem Cell and Developmental Neurobiology

Lab VIB-KU Leuven Center for Brain & Disease Research

Department of Neurosciences, Leuven Brain Institute IRIBHM / ULB Neuroscience Institute

O&N5 Herestraat 49 box 602 | 3000 Leuven | Belgium

Email: pierre.vanderhaeghen@kuleuven.be - <https://pvdhlab.org>

T +32 16 3 77038

F +32 16 3 30827

Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- LIBÉ-PHILIPPOT B, LEJEUNE A, WIERDA K, VLAEMINCK I, BECKERS S, GASPARIUNAITE V, BILHEU A, NYITRAI H, VENNEKENS KM, BIRD TW, SOTO D, DENNIS MY, COMOLETTI D, THEYS T, DE WIT J, VANDERHAEGHEN P.

LRRC37B is a human modifier of voltage-gated sodium channels and axon excitability in cortical neurons.

Cell (2023) 186, 5766-5783. IF: 38 –

Summary

The enhanced cognitive abilities characterizing the human species result from specialized features of neurons and circuits. Here, we report that the hominid-specific gene *LRRC37B* encodes a receptor expressed in human cortical pyramidal neurons (CPNs) and selectively localized to the axon initial segment (AIS), the subcellular compartment triggering action potentials. Ectopic expression of *LRRC37B* in mouse CPNs *in vivo* leads to reduced intrinsic excitability, a distinctive feature of some classes of human CPNs. Molecularly, *LRRC37B* binds to the secreted ligand FGF13A and to the voltage-gated sodium channel (Nav) -subunit SCN1B. *LRRC37B* concentrates inhibitory effects of FGF13A on Nav channel function, thereby reducing excitability, specifically at the AIS level. Electrophysiological recordings in adult human cortical slices reveal lower neuronal excitability in human CPNs expressing *LRRC37B*. *LRRC37B* thus acts as a species-specific modifier of human neuron excitability, linking human genome and cell evolution, with important implications for human brain function and diseases.

Keywords: human brain evolution, gene duplicates, neuronal excitability, *LRRC37*, FGF13, voltage-gated channels, axon initial segment, cerebral cortex, SCN1B

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VIB (#C0401 to F.R. and J.S.), KU Leuven (postdoctoral fellowship PDM PDMT2/22/059 to K.K.), the Stichting Alzheimer Onderzoek/Fondation Recherche Alzheimer (SAO-FRA 2020/0013 and SAO-FRA 2022/0020 to N.L.), the RWJ Foundation (#74260 to the Child Health Institute of New Jersey), the National Science Foundation award (#1755189 to D.C.), and the National Institutes of Health (DP2MH119424 to D.C.S. and M.Y.D.).

- IWATA, R., CASIMIR, P., ERKOL, E., BOUBAKAR, L., PLANQUE, M., DITKOWSKA, M., VINTS, K., GASPARIUNAITE, V., BIRD, M., CORTHOUT, N., VERMEERSCH, P., DAVIE, K., GOUNKO, V., AERTS, S., GHESQUIÈRE, B., FENDT, S-M, VANDERHAEGHEN P.

Mitochondria Metabolism Sets the Species-Specific Tempo of Neuronal Development.

Science (2023) 379, eabn4705 DOI: 10.1126/science.abn4705. IF: 41 –

Abstract

Neuronal development in the human cerebral cortex is considerably prolonged compared with that of other mammals. We explored whether mitochondria influence the species-specific timing of cortical neuron maturation. By comparing human and mouse cortical neuronal maturation at high temporal and cell resolution, we found a slower mitochondria development in human cortical neurons compared with that in the mouse, together with lower mitochondria metabolic activity, particularly that of oxidative phosphorylation. Stimulation of mitochondria metabolism in human neurons resulted in accelerated development *in vitro* and *in vivo*, leading to maturation of cells weeks ahead of time, whereas its inhibition in mouse neurons led to decreased rates of maturation. Mitochondria are thus important regulators of the pace of neuronal development underlying human-specific brain neoteny.

Acknowledgments

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- VANDERHAEGHEN P, FRANCK POLLEUX.

Developmental mechanisms underlying the evolution of human cortical circuits

Nat. Rev. Neurosci. (2023) 24, 213-232 IF: 39 –

Abstract

The brain of modern humans has evolved remarkable computational abilities that enable higher cognitive functions. These capacities are tightly linked to an increase in the size and connectivity of the cerebral cortex, which is thought to have resulted from evolutionary changes in the mechanisms of cortical development. Convergent progress in evolutionary genomics, developmental biology and neuroscience has recently enabled the identification of genomic changes that act as human-specific modifiers of cortical development. These modifiers influence most aspects of corticogenesis, from the timing and complexity of cortical neurogenesis to synaptogenesis and the assembly of cortical circuits. Mutations of human-specific genetic modifiers of corticogenesis have started to be linked to neurodevelopmental disorders, providing evidence for their physiological relevance and suggesting potential relationships between the evolution of the human brain and its sensitivity to specific diseases.

Acknowledgments

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- VAN HEURCK R, WOJNO M, SUZUKI IK, VELEZ-BRAVO FD, BONNEFONT J, ERKOL E, NGUYEN DT, HERPOEL A, BILHEU A, LEDENT C, VANDERHAEGHEN P.

CROCCP2 acts as a human-specific modifier of cilia dynamics and mTOR signalling to promote expansion of cortical progenitors

Neuron (2023) 4;111(1):65-80. IF: 18

Abstract

The primary cilium is a central signaling component during embryonic development. Here we focus on CROCCP2, a hominid-specific gene duplicate from ciliary rootlet coiled coil (CROCC), also known as rootletin, that encodes the major component of the ciliary rootlet. We find that CROCCP2 is highly expressed in the human fetal brain and not in other primate species. CROCCP2 gain of function in the mouse embryonic cortex and human cortical cells and organoids results in decreased ciliogenesis and increased cortical progenitor amplification, particularly basal progenitors. CROCCP2 decreases ciliary dynamics by inhibition of the IFT20 ciliary trafficking protein, which then impacts neurogenesis through increased mTOR signaling. Loss of function of CROCCP2 in human cortical cells and organoids leads to increased ciliogenesis, decreased mTOR signaling, and impaired basal progenitor amplification. These data identify CROCCP2 as a human-specific modifier of cortical neurogenesis that acts through modulation of ciliary dynamics and mTOR signaling.

Keywords: CROCC; CROCCP2; cerebral cortex; cilia; evolution; human brain development; mTOR; neurogenesis; rootlet; rootletin.

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Publications in 2024 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- IWATA R, VANDERHAEGHEN P.

Metabolic mechanisms of species-specific developmental tempo

Dev. Cell (2024) 59, 1628-1639. IF: 14

Abstract

Development consists of a highly ordered suite of steps and transitions, like choreography. Although these sequences are often evolutionarily conserved, they can display species variations in duration and speed, thereby modifying final organ size or function. Despite their evolutionary significance, the mechanisms underlying species-specific scaling of developmental tempo have remained unclear. Here, we will review recent findings that implicate global cellular mechanisms, particularly intermediary and protein metabolism, as species-specific modifiers of developmental tempo. In various systems, from somitic cell oscillations to neuronal development, metabolic pathways display species differences. These have been linked to mitochondrial metabolism, which can influence the species-specific speed of developmental transitions. Thus, intermediary metabolic pathways regulate developmental tempo together with other global processes, including proteostasis and chromatin remodeling. By linking metabolism and the evolution of developmental trajectories, these findings provide opportunities to decipher how species-specific cellular timing can influence organism fitness

Acknowledgments

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- LIBÉ-PHILIPPOT B, IWATA R, RECUPERO AJ, WIERDA K, DITKOWSKA M, GASPARIUNAITE V, VERMAERCKE B, PEZE-HEIDSIECK E, REMANS D, CHARRIER C, POLLEUX F, VANDERHAEGHEN P.

Human synaptic neoteny requires species-specific balancing of SRGAP2-SYNGAP1 cross-inhibition.

Neuron (2024) 112, 3602-3617. IF: 18

Abstract

Human-specific (HS) genes have been implicated in brain evolution, but their impact on human neuron development and diseases remains unclear. Here, we study SRGAP2B/C, two HS gene duplications of the ancestral synaptic gene SRGAP2A, in human cortical pyramidal neurons (CPNs) xenotransplanted in the mouse cortex. Downregulation of SRGAP2B/C in human CPNs led to strongly accelerated synaptic development, indicating their requirement for the neoteny that distinguishes human synaptogenesis. SRGAP2B/C genes promoted neoteny by reducing the synaptic levels of SRGAP2A, thereby increasing the postsynaptic accumulation of the SYNGAP1 protein, encoded by a major intellectual disability/autism spectrum disorder (ID/ ASD) gene. Combinatorial loss-of-function experiments in vivo revealed that the tempo of synaptogenesis is set by the reciprocal antagonism between SRGAP2A and SYNGAP1, which in human CPNs is tipped toward neoteny by SRGAP2B/C. Thus, HS genes can modify the phenotypic expression of genetic mutations leading to ID/ASD through the regulation of human synaptic neoteny

Acknowledgments

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- ASSENDORP N, FOSSATI M, LIBÉ-PHILIPPOT B, CHRISTOPOULOU E, DEPP M, RAPONE R, DINGLI F, LOEW D, VANDERHAEGHEN P, CHARRIER C.

CTNND2 moderates the pace of synaptic maturation and links human evolution to synaptic neoteny.

Cell Reports (2024) 43, 114797. IF: 8

Abstract

Human-specific (HS) genes have been implicated in brain evolution, but their impact on human neuron development and diseases remains unclear. Here, we study SRGAP2B/C, two HS gene duplications of the ancestral synaptic gene SRGAP2A, in human cortical pyramidal neurons (CPNs) xenotransplanted in the mouse cortex. Downregulation of SRGAP2B/C in human CPNs led to strongly accelerated synaptic development, indicating their requirement for the neoteny that distinguishes human synaptogenesis. SRGAP2B/C genes promoted neoteny by reducing the synaptic levels of SRGAP2A, thereby increasing the postsynaptic accumulation of the SYNGAP1 protein, encoded by a major intellectual disability/autism spectrum disorder (ID/ ASD) gene. Combinatorial loss-of-function experiments in vivo revealed that the tempo of synaptogenesis is set by the reciprocal antagonism between SRGAP2A and SYNGAP1, which in human CPNs is tipped toward neoteny by SRGAP2B/C. Thus, HS genes can modify the phenotypic expression of genetic mutations leading to ID/ASD through the regulation of human synaptic neoteny

Acknowledgments

We thank members of the P.V. laboratory for helpful discussions and precious help, including Niels Vidal (CBD). We thank patients for their participation in the study and Anai's van Hoylandt (UZLeuven) for assistance. We thank Joris de Wit laboratory (CBD) for excellent advice as well as Bart de Strooper and Ludo Van Den Bosch laboratories (CBD) for sharing their chemiluminescence imaging systems. Some of the images were acquired on Zeiss LSM880 supported by Hercules AKUL/15/37_GOH1816N and FWO G.0929.15 to Pieter Vanden Berghe, KU Leuven, whom we also thank for training and technical advice. Some of the images were acquired with support from the Zuckerman Institute's Cellular Imaging Platform. The authors

gratefully acknowledge the VIB Bio Imaging Core for their support and assistance in this work. Drawings were created using BioRender.com. This work was funded by grants from the European Research Council (GENDEVOCORTEX), C1 KU Leuven, the EOS Programme, EPINEURODEVO Grant ERANET NEURON, the Belgian FWO and FRS/FNRS, EU network NSC-Reconstruct, the Generet Foundation, and the Belgian Queen Elizabeth Foundation (to P.V.). B.L.-P. was supported by a postdoctoral fellowship of the FWO (12V1219N). Work in the Polleux lab is supported by the NIH (R35 NS127232) and a NOMIS Foundation Research Project. A.J.R. was supported by the NIH/NIGMS (T32 GM145440). Work in the C.C. lab is supported by Inserm, CNRS, ENS, labex Memolife, and the European Research Council (SYNPATh).

- CASIMIR P, IWATA R, VANDERHAEGHEN P.

Linking Mitochondria Metabolism, Developmental Timing, and Human Brain Evolution. Curr. Opin.

Gen. & Dev. (2024) 86:102182. IF: 5

Abstract

Changes in developmental timing are an important factor of evolution in organ shape and function. This is particularly striking for human brain development, which, compared with other mammals, is considerably prolonged at the level of the cerebral cortex, resulting in brain neoteny. Here, we review recent findings that indicate that mitochondria and metabolism contribute to species differences in the tempo of cortical neuron development. Mitochondria display species-specific developmental timeline and metabolic activity patterns that are highly correlated with the speed of neuron maturation. Enhancing mitochondrial activity in human cortical neurons results in their accelerated maturation, while its reduction leads to decreased maturation rates in mouse neurons. Together with other global and gene-specific mechanisms, mitochondria thus act as a cellular hourglass of neuronal developmental tempo and may thereby contribute to species-specific features of human brain ontogeny.

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- VERMAERCKE B, IWATA R, WEIRDA K, BOUBAKAR L, RODRIGUEZ P, DITKOWSKA M, BONIN V, VANDERHAEGHEN P.

SYNGAP1 deficiency disrupts neoteny in xenotransplanted human cortical neurons in vivo.

Neuron (2024) 112, 3058-3068. IF: 18

Abstract

Human brain ontogeny is characterized by a considerably prolonged neotenic development of cortical neurons and circuits. Neoteny is thought to be essential for the acquisition of advanced cognitive functions, which are typically altered in intellectual disability (ID) and autism spectrum disorders (ASDs). Human neuronal neoteny could be disrupted in some forms of ID and/or ASDs, but this has never been tested. Here, we use xenotransplantation of human cortical neurons into the mouse brain to model SYNGAP1 haploinsufficiency, one of the most prevalent genetic causes of ID/ASDs. We find that SYNGAP1-deficient human neurons display strong

acceleration of morphological and functional synaptic formation and maturation alongside disrupted synaptic plasticity. At the circuit level, SYNGAP1-haploinsufficient neurons display precocious acquisition of responsiveness to visual stimulation months ahead of time. Our findings indicate that SYNGAP1 is required cell autonomously for human neuronal neoteny, providing novel links between human-specific developmental mechanisms and ID/ASDs.

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- SERGIU P PAȘCA · PAOLA ARLOTTA · HELEN S BATEUP · J GRAY CAMP · SILVIA CAPPELLO · FRED H GAGE · JÜRGEN A KNOBLICH · ARNOLD R KRIEGSTEIN · MADELINE A LANCASTER · GUO-LI MING · GAIA NOVARINO · HIDEYUKI OKANO · MALIN PARMAR · IN-HYUN PARK · ORLY REINER · HONGJUN SONG · LORENZ STUDER · JUN TAKAHASHI · SALLY TEMPLE · GIUSEPPE TESTA · BARBARA TREUTLEIN · FLORA M VACCARINO · **PIERRE VANDERHAEGHEN** · TRACY YOUNG-PEARSE

A framework for neural organoids, assembloids and transplantation studies

T. Nature (2025) 639, 315–320. doi: 10.1038/s41586-024-08487-6. IF: 48

Affiliations ExpandPMID: 39653126 - DOI: 10.1038/s41586-024-08487-6

Abstract

As the field of neural organoids and assembloids expands, there is an emergent need for guidance and advice on designing, conducting and reporting experiments to increase the reproducibility and utility of these models. In this Perspective, we present a framework for the experimental process that encompasses ensuring the quality and integrity of human pluripotent stem cells, characterizing and manipulating neural cells *in vitro*, transplantation techniques and considerations for modelling human development, evolution and disease. As with all scientific endeavours, we advocate for rigorous experimental designs tailored to explicit scientific questions as well as transparent methodologies and data sharing to provide useful knowledge for current research practices and for developing regulatory standards.

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Prof. dr. Veerle Baekelandt

Laboratory for Neurobiology and Gene Therapy

Division of Molecular Medicine KU.Leuven

Faculty of Medicine Kapucijnenvoer 33 VCTB+5

B-3000 Leuven

Belgium

Tel.: +32 16 37 40 61

Fax: +32 16 33 63 36

E-mail: Veerle.Baekelandt@kuleuven.be

Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- CABEZUDO D, TSAFARAS G, VAN ACKER E, VAN DEN HAUTE C, BAEKELANDT V. (2023)
Mutant LRRK2 exacerbates immune response and neurodegeneration in a chronic model of experimental colitis.
Acta Neuropathologica, 146(2):245-261. (IF 15.9, cit 4)

Abstract

The link between the gut and the brain in Parkinson's disease (PD) pathogenesis is currently a subject of intense research. Indeed, gastrointestinal dysfunction is known as an early symptom in PD and inflammatory bowel disease (IBD) has recently been recognised as a risk factor for PD. The leucine-rich repeat kinase 2 (LRRK2) is a PD- and IBD-related protein with highest expression in immune cells. In this study, we provide evidence for a central role of LRRK2 in gut inflammation and PD. The presence of the gain-of-function G2019S mutation significantly increases the disease phenotype and inflammatory response in a mouse model of experimental colitis based on chronic dextran sulphate sodium (DSS) administration. Bone marrow transplantation of wild-type cells into G2019S knock-in mice fully rescued this exacerbated response, proving the key role of mutant LRRK2 in immune cells in this experimental colitis model. Furthermore, partial pharmacological inhibition of LRRK2 kinase activity also reduced the colitis phenotype and inflammation. Moreover, chronic experimental colitis also induced neuroinflammation and infiltration of peripheral immune cells into the brain of G2019S knock-in mice. Finally, combination of experimental colitis with overexpression of -synuclein in the substantia nigra aggravated motor deficits and dopaminergic neurodegeneration in G2019S knock-in mice. Taken together, our results link LRRK2 with the immune response in colitis and provide evidence that gut inflammation can impact brain homeostasis and contribute to neurodegeneration in PD.

Keywords: Alpha-synuclein; Inflammation; Inflammatory bowel disease; LRRK2; Parkinson's disease.

Funding

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- No publication in 2024

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- TSAFARAS, G., CABEZUDO, D., WETZELS, L., TSAKOGIAS, I., ABEY, A., BENTEA, E., SANCHIZ-CALVO, M., VAN DEN HAUTE, C., WADE-MARTINS, R. AND BAEKELANDT, V. (2025)

The G2019S LRRK2 mutation exacerbates alpha-synuclein and tau neuropathology through divergent pathways in Parkinson's disease models.

Acta Neuropathol 2025 Nov 11;150(1):51. doi: 10.1007/s00401-025-02956-6.150, 51. (Q1 Neurosciences, IF 9.3)

Abstract

Aggregated α -synuclein (Syn) is a pathological hallmark of Parkinson's disease (PD), yet other protein aggregates, including tau, are commonly observed in PD brains. This suggests that PD is not solely a synucleinopathy but may involve multiple, coexisting proteinopathies. Mutations in LRRK2, particularly the G2019S (GS), are the most common cause of familial PD. LRRK2-PD has been associated with both Syn and tau pathology; however the mechanistic links between LRRK2 dysfunction and protein aggregation remain incompletely defined. Here we opted to investigate whether LRRK2 contributes to Syn and tau pathology through common molecular pathways or via distinct cellular mechanisms. Viral vector-mediated Syn overexpression in GS LRRK2 knock-in mice led to enhanced dopaminergic neurodegeneration, increased phosphorylated Syn levels, pronounced neuroinflammation, and accumulation of lysosomal proteins, suggesting impaired Syn clearance and immune activation as key drivers. Human iPSC-derived dopaminergic neurons from GS LRRK2 PD patients mirrored these findings. In contrast viral vector-mediated overexpression of tau in GS LRRK2 knock-in mice promoted tau phosphorylation but did not significantly affect neuroinflammation, lysosomal markers, or neurodegeneration, indicating a primarily cell-autonomous mechanism. Our results reveal a mechanistic divergence in how GS LRRK2 impacts Syn and tau pathologies, supporting the notion that LRRK2 kinase activity contributes to PD pathogenesis through different pathways, thereby highlighting its potential as a therapeutic target in both familial and sporadic PD.

Keywords: Alpha-synuclein; LRRK2; Parkinson's disease; Tau.

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Prof. dr. Thomas Voets

Laboratory of Ion Channel Research VIB-KU Leuven

Center for Brain & Disease Research KU Leuven,

Department of Cellular and Molecular Medicine Herestraat 49 bus 801 3000 Leuven

Tel: +32 16 33 02 17 Thomas.voets@kuleuven.vib.be

Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- ALOI, V. D., PINTO, S., VAN BREE, R., LUYTEN, K., VOETS, T., & VRIENS, J. (2023).

TRPM3 as a novel target to alleviate acute oxaliplatin-induced peripheral neuropathic pain.

Pain, 164(9), 2060-2069. <https://doi.org/10.1097/j.pain.0000000000002906> –

Abstract

Chemotherapy-induced peripheral neuropathic pain (CIPNP) is an adverse effect observed in up to 80% of patients of cancer on treatment with cytostatic drugs including paclitaxel and oxaliplatin. Chemotherapy-induced peripheral neuropathic pain can be so severe that it limits dose and choice of chemotherapy and has significant negative consequences on the quality of life of survivors. Current treatment options for CIPNP are limited and unsatisfactory. TRPM3 is a calcium-permeable ion channel functionally expressed in peripheral sensory neurons involved in the detection of thermal stimuli. Here, we focus on the possible involvement of TRPM3 in acute oxaliplatin-induced mechanical allodynia and cold hypersensitivity. In vitro calcium microfluorimetry and whole-cell patch-clamp experiments showed that TRPM3 is functionally upregulated in both heterologous and homologous expression systems after acute (24 hours) oxaliplatin treatment, whereas the direct application of oxaliplatin was without effect. In vivo behavioral studies using an acute oxaliplatin model for CIPNP showed the development of cold and mechano hypersensitivity in control mice, which was lacking in TRPM3 deficient mice. In addition, the levels of protein ERK, a marker for neuronal activity, were significantly reduced in dorsal root ganglion neurons derived from TRPM3 deficient mice compared with control after oxaliplatin administration. Moreover, intraperitoneal injection of a TRPM3 antagonist, isosakuranetin, effectively reduced the oxaliplatin-induced pain behavior in response to cold and mechanical stimulation in mice with an acute form of oxaliplatin-induced peripheral neuropathy. In summary, TRPM3 represents a potential new target for the treatment of neuropathic pain in patients undergoing chemotherapy.

- BECKER, L. L., HORN, D., BOSCHANN, F., VAN HOEYMISSSEN, E., VOETS, T., VRIENS, J., PRAGER, C., & KAINDL, A. M. (2023).

Primidone improves symptoms in TRPM3-linked developmental and epileptic encephalopathy with spike-and-wave activation in sleep.

Epilepsia, 64(5), e61-e68. <https://doi.org/10.1111/epi.17586> –

Abstract

Developmental and epileptic encephalopathy with continuous spike-and-wave activation in sleep (CSWS) or DEE-SWAS is an age-dependent disease, often accompanied by a decline in cognitive abilities. Early successful treatment of CSWS is associated with a better cognitive outcome. We retrospectively analyzed the clinical, electrophysiological, radiological, and genetic data of children with DEE-SWAS associated with melastatin-related transient receptor type 3 gene (TRPM3) missense variants. We report two unrelated children with pharmacoresistant DEE-SWAS and developmental delay/regression and different heterozygous de novo missense variants in the TRPM3 gene (NM_001366145.2; c.3397 T > C/p.Ser1133Pro, c.2004G > A/p.Val1002Met). The variant p.Val1002Met (previously known as p.Val990Met or p.Val837Met) and p.Ser1133Pro were recently shown to result in a gain-of-function effect. Based on this finding, previous drug resistance, and the experimentally demonstrated inhibitory effect of primidone on TRPM3, we initiated an individualized therapy with this drug. In both children,

developmental regression was stopped, psychomotor development improved, and CSWS was no longer detectable. To our knowledge, this is the first report of a treatment with primidone in TRPM3-associated CSWS. Our results highlight the importance of early genetic diagnosis in patients with epilepsy and the possibility of precision medicine, which should be considered in the future in individuals with a TRPM3-linked DEE-SWAS.

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Gain-of-function variants in the ion channel gene TRPM3 underlie a spectrum of neurodevelopmental disorders.

Elife, 12. <https://doi.org/10.7554/eLife.81032> –

Abstract

TRPM3 is a temperature- and neurosteroid-sensitive plasma membrane cation channel expressed in a variety of neuronal and non-neuronal cells. Recently, rare de novo variants in *TRPM3* were identified in individuals with developmental and epileptic encephalopathy, but the link between TRPM3 activity and neuronal disease remains poorly understood. We previously reported that two disease-associated variants in TRPM3 lead to a gain of channel function. Here, we report a further 10 patients carrying one of seven additional heterozygous *TRPM3* missense variants. These patients present with a broad spectrum of neurodevelopmental symptoms, including global developmental delay, intellectual disability, epilepsy, musculo-skeletal anomalies, and altered pain perception. We describe a cerebellar phenotype with ataxia or severe hypotonia, nystagmus, and cerebellar atrophy in more than half of the patients. All disease-associated variants exhibited a robust gain-of-function phenotype, characterized by increased basal activity leading to cellular calcium overload and by enhanced responses to the neurosteroid ligand pregnenolone sulfate when co-expressed with wild-type TRPM3 in mammalian cells. The antiseizure medication primidone, a known TRPM3 antagonist, reduced the increased basal activity of all mutant channels. These findings establish gain-of-function of TRPM3 as the cause of a spectrum of autosomal dominant neurodevelopmental disorders with frequent cerebellar involvement in humans and provide support for the evaluation of TRPM3 antagonists as a potential therapy.

Keywords: TRPM3; cell biology; cerebellar atrophy; epilepsy; gain-of-function; human; intellectual disability; neurodevelopment; neuroscience.

Funding

Queen Elisabeth Medical Foundation for Neurosciences: Thomas Voets

- DANILUK, J., & VOETS, T. (2023).

pH-dependent modulation of TRPV1 by modality-selective antagonists.

Br J Pharmacol, 180(21), 2750-2761.

<https://doi.org/10.1111/bph.16173> –

Abstract

Background and purpose: Antagonists of TRPV1 that inhibit all activation modes cause hyperthermia, hampering their medical use as novel analgesics. TRPV1 antagonists that do not (fully) inhibit responses to low pH do not cause hyperthermia, but it remains incompletely understood how such antagonists affect channel gating. We tested the hypothesis that pH-sparing antagonists act in a modality-selective manner on TRPV1, differentially affecting

channel activation by protons and capsaicin.

Experimental approach: Using whole-cell patch-clamp and calcium imaging to measure channel activity in cells expressing wild type human TRPV1 or the pH-insensitive mutant F660A. Responses to protons and capsaicin were measured at different pH values in the presence of antagonists that reportedly partially spare (A-1165442) or potentiate (AMG7905) acid-evoked channel activation.

Key results: At pH 5.5, A-1165442 was equipotent at blocking acid- and capsaicin-evoked responses of wild type TRPV1. Its potency to inhibit acid-evoked responses was attenuated at pH $\leq$ 5.0. AMG7905, at a concentration (1 μ M) that fully inhibits capsaicin-evoked responses, potentiated proton-evoked (pH 5.5) responses of wild type TRPV1. In the F660A mutant, the inhibitory efficacy of A-1165442 and AMG7905 towards capsaicin-evoked responses was reduced at lower pH values and AMG7905 acted as a partial agonist.

Conclusion and implications: Our findings show that A-1165442 and AMG7905 interact in a pH-dependent manner with TRPV1, but this pH dependence is not strictly modality-selective. Reduced TRPV1 antagonism at acidic pH may limit analgesic efficacy in injured tissue and needs to be considered in models explaining the effects of antagonists on core body temperature.

Keywords: TRPV1; hyperthermia; modality-selective antagonists; pain.

Acknowledgments

We thank Melissa Benoit and Annelies Janssens for technical assistance and all the members of the Laboratory of Ion Channel Research for helpful discussion. This work was supported by grants (to T.V.) from the Research Foundation - Flanders (FWO; G0B9520N), the Research Council of KU Leuven (C2-TRP), the Queen Elisabeth Medical Foundation for Neurosciences and the VIB.

- LUYTS, N., DANILUK, J., FREITAS, A. C. N., BAZELI, B., JANSSENS, A., MULIER, M., EVERAERTS, W., & VOETS, T. (2023).

Inhibition of TRPM8 by the urinary tract analgesic drug phenazopyridine.

Eur J Pharmacol, 942, 175512. <https://doi.org/10.1016/j.ejphar.2023.175512>

Abstract

Background: and purpose: Phenazopyridine (PAP) is an over-the-counter drug widely used to provide symptomatic relief of bladder pain in conditions such as cystitis or bladder pain syndrome (BPS). Whereas the analgesic effect of PAP has been attributed to a local effect on the mucosa of the lower urinary tract (LUT), the molecular targets of PAP remain unknown. We investigated the effect of PAP on pain-related Transient Receptor Potential (TRP) channels expressed in sensory neurons that innervate the bladder wall.

Experimental approach: The effects of PAP on the relevant TRP channels (TRPV1, TRPA1, TRPM8, TRPM3) expressed in HEK293 or CHO cells was investigated using Fura-2-based calcium measurements and whole-cell patch-clamp recordings. Activity of PAP on TRPM8 was further analysed using Fura-2-based calcium imaging on sensory neurons isolated from lumbosacral dorsal root ganglia (DRG) of mice.

Key results: PAP rapidly and reversibly inhibits responses of TRPM8 expressed in HEK293 cells to cold and menthol, with IC₅₀ values between 2 and 10 μ M. It acts by shifting the voltage dependence of channel activation towards positive potentials, opposite to the effect of menthol. PAP also inhibits TRPM8-mediated, menthol-evoked calcium responses in lumbosacral DRG neurons. At a concentration of 10 μ M, PAP did not significantly affect TRPA1, TRPV1, or TRPM3.

Conclusion and implications: PAP inhibits TRPM8 in a concentration range consistent with PAP levels in the urine of treated patients. Since TRPM8 is expressed in bladder afferent neurons and upregulated in patients with painful bladder disorders, TRPM8 inhibition may underlie the

analgesic activity of PAP.

Keywords: Analgesia; Molecular target; Phenazopyridine; TRPM8; Urinary tract.

Acknowledgments

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Publications in 2024 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- (*: shared last and corresponding authors) –

TOTH BI, BAZELI B, JANSSENS A, LISZTES E, RACSKO M, KELEMEN B, HERCZEG M, NAGY TM, MITRA A, BIRO T, VOETS T:

Direct modulation of TRPM8 ion channels by rapamycin and analog macrolide immunosuppressants.

eLife (2024), in press. –

- ROELEN R, PEIGNEUR ANF, VOETS T, VRIENS J:

Neurodevelopmental disorders caused by variants in TRPM3.

Biochim Biophys Acta Mol Cell Res (2024): 119709

Abstract

Developmental and epileptic encephalopathies (DEE) are a broad and varied group of disorders that affect the brain and are characterized by epilepsy and comorbid intellectual disability (ID). These conditions have a broad spectrum of symptoms and can be caused by various underlying factors, including genetic mutations, infections, and other medical conditions. The exact cause of DEE remains largely unknown in the majority of cases. However, in around 25 % of patients, rare nonsynonymous coding variants in genes encoding ion channels, cell-surface receptors, and other neuronally expressed proteins are identified. This review focuses on a subgroup of DEE patients carrying variations in the gene encoding the Transient Receptor Potential Melastatin 3 (TRPM3) ion channel, where recent data indicate that gain-of-function of TRPM3 channel activity underlies a spectrum of dominant neurodevelopmental disorders.

Keywords: DEE; Neurodevelopmental disorders; TRP channel; TRPM3 variants.

Funding

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Publications in 2025 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- TOTH, B. I., BAZELI, B., JANSSENS, A., LISZTES, E., RACSKO, M., KELEMEN, B., HERCZEG, M., NAGY, T. M., KOVER, K. E., MITRA, A., BORICS, A., BIRO, T. & VOETS, T.

Direct modulation of TRPM8 ion channels by rapamycin and analog macrolide immunosuppressants.

Elife 13 (2025). Sep 30:13:RP97341.

doi: 10.7554/eLife.97341.<https://doi.org/10.7554/eLife.97341>. (IF: 6.4; Q1).

Abstract

Rapamycin (sirolimus), a macrolide compound isolated from the bacterium *Streptomyces hygroscopicus*, is widely used as oral medication for the prevention of transplant rejection and the treatment of lymphangioleiomyomatosis. It is also incorporated in coronary stent coatings to prevent restenosis and in topical preparations for the treatment of skin disorders. Rapamycin's in vivo activities are generally ascribed to its binding to the protein FKBP12, leading to potent inhibition of the mechanistic target of rapamycin kinase (mTOR) by the FKBP12-rapamycin complex. The specific rapamycin-induced interaction between domains from mTOR and FKBP12 is also frequently employed in cell biological research, for rapid chemically-induced protein dimerization strategies. Here, we show that rapamycin activates TRPM8, a cation channel expressed in sensory nerve endings that serves as the primary cold sensor in mammals. Using a combination of electrophysiology, Saturation Transfer Triple-Difference (STTD) NMR spectroscopy, and molecular docking-based targeted mutagenesis, we demonstrate that rapamycin directly binds to human TRPM8. We identify a rapamycin-binding site in the groove between voltage sensor-like domain and the pore domain, distinct from the interaction sites of cooling agents and known TRPM8 agonists menthol and icilin. Related macrolide immunosuppressants act as partial TRPM8 agonists, competing with rapamycin for the same binding site. These findings identify a novel molecular target for rapamycin and provide new insights into the mechanisms of TRPM8 activation, which may assist in the development of therapies targeting this ion channel. Moreover, our findings also indicate that caution is needed when using molecular approaches based on rapamycin-induced dimerization to study ion channel regulation.

Keywords: Rapamycin; TRP ion channels; TRPM8; human; ion channel gating; mouse; neuroscience; structure-function.

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- DESEURE, K., DALLALI, I., PINTO, S., LUYTEN, K., SEGAL, A., VAN RANST, N., ROELEN, R., CORBETT, S., MURRAY, S., PERSOONS, E., HANS, G., VRIENS, J. & **VOETS, T.**

TRPM3 mediates spontaneous pain and mechanical allodynia in a mouse model of chronic orofacial neuropathy.

Cell Reports Medicine (in press). (IF: 10.6; Q1) –

Cell Rep Med 2026 Mar 17;7(3):102645. doi: 10.1016/j.xcrm.2026.102645. Epub 2026 Mar 9.

Abstract

Trigeminal nerve injury can lead to chronic and difficult-to-treat orofacial neuropathic pain. Here, we uncover a key role for the cation channel TRPM3 in the chronic constriction injury of the infraorbital nerve (IoN-CCI) mouse model of trigeminal neuropathic pain. Wild-type (WT) mice develop spontaneous pain and mechanical allodynia for up to 6 weeks following IoN-CCI, whereas *Trpm3*^{-/-} mice do not develop such symptoms. Using longitudinal RNA sequencing (RNA-seq) analysis, we obtain a detailed time course of transcriptome alterations in trigeminal ganglia during progression of the IoN-CCI model; notably, gene expression regulation is not different between WT and *Trpm3*^{-/-} mice. Two structurally distinct TRPM3 antagonists, primidone and isosakuranetin, effectively reverse spontaneous pain and mechanical allodynia, whereas mavatrep, a potent TRPV1 antagonist, is without analgesic effect. These data indicate that TRPM3 is essential for ongoing pain and allodynia following trigeminal nerve injury, making it a potential target for treating trigeminally mediated neuropathic pain.

Keywords: TRP channels; TRPM3; neuropathic pain; trigeminal neuron.

Acknowledgments

We thank all members of the Laboratory of Ion Channel Research for support and discussions. This work was supported by grants from the Research Foundation Flanders (FWO; GoB9520N, GoB7620N, Go55124N, and Scientific Network W000221N to T.V. and G.084515N and G.0B1819N to J.V.), the KU Leuven (C24M/21/028 to T.V. and C3/21/049 to J.V. and T.V.), **the Queen Elisabeth Medical Foundation for Neurosciences (to T.V.)**, and the VIB (to T.V.). This research has been conducted using the UK Biobank Resource under application number 103552.

- BAZELI, B., SHKHUMATOV, A. V., SCHENCK, S., VANHERCK, J. C., JANSSENS, A., SPIESER, S. A., MARCHAND, D., ROELEN, R., CHALTIN, P., MARCHAND, A., VRIENS, J., **VOETS, T.*** & BRUNNER, J. D.*

Stereoselectivity and functional plasticity of a common ligand-binding pocket in TRPM3.

Nature Communications (in press). (IF: 15.7; Q1) –

Nat Commun 2026 Apr 1;17(1):4556. doi: 10.1038/s41467-026-71226-0.

Affiliations Expand

PMID: 41922314 - PMCID: PMC13194908 - DOI: 10.1038/s41467-026-71226-0

Abstract

The transient receptor potential melastatin 3 (TRPM3) channel is a key mediator of peripheral pain signaling, and pathogenic mutations in TRPM3 are linked to neurodevelopmental delay and epilepsy. Despite the therapeutic promise of TRPM3 modulators, the molecular mechanisms by which ligands modulate channel gating remain poorly understood. Here, we combine cryo-electron microscopy (cryo-EM) with functional analyses to characterize a promiscuous ligand-binding pocket formed by transmembrane helices S1-S4. This pocket accommodates several chemically diverse plant-derived and synthetic agonists and antagonists. We show stereoselectivity of TRPM3 for the (R)-enantiomer of the flavonoid antagonist isosakuranetin and the (R)-enantiomer of the synthetic agonist CIM0216. Mutations within this pocket—including variants identified in patients—alter ligand affinity and, in some cases, invert the functional outcome of ligand binding. These findings reveal the stereoselectivity and functional plasticity of the TRPM3 ligand-binding pocket, highlighting how subtle changes in the molecular interactions can produce divergent effects on channel gating, with important ramifications for TRPM3-targeted drug development and therapy.

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- ROBBEN, S., DAVIDSON, P., RODRIGUES RIBEIRO, R.S., **VOETS, T.**

A high-throughput assay for the measurement of Ca²⁺ oscillations and insulin release from uniformly sized -cell spheroids

eLife (in press). (IF: 6.4#; Q1) – Reviewed Preprint v1 • March 4, 2026 Not revised

Cell Biology: <https://doi.org/10.7554/eLife.110428.1>

Abstract

Diabetes mellitus is a rapidly growing global health challenge, necessitating the development of more effective anti-diabetic therapies, including drugs that improve insulin release from pancreatic β -cells. Traditional high-throughput screening methods typically rely on 2D β -cell cultures, but such cultures do not mimic the 3D organisation and cell-to-cell communication of cells in pancreatic islets of Langerhans. Existing 3D β -cell culture models are hindered by high costs, technical complexity, and limited compatibility with high-throughput screening platforms. In this work, we developed an approach for generating 19 homogeneously shaped pancreatic cell spheroids in each well of a 96-well plate, using micropatterned polyethylene glycol (PEG)-based hydrogels and MIN6 insulinoma cells. The uniform shape and positioning of the individual spheroids enabled the simultaneous, real-time imaging of Ca²⁺ signals in up to 1824 independent spheroids in response to glucose and various test compounds. Using this approach, we show that increasing glucose causes concentration-dependent Ca²⁺ oscillations in individual spheroids, that these Ca²⁺ oscillations are sensitive to modulators of ATP-sensitive K⁺ channels, and that the frequency of Ca²⁺ oscillations correlate with insulin secretion. Finally, we demonstrate that the neurosteroid pregnenolone sulphate, an agonist of the cation channel TRPM3, increases the frequency of glucose-induced Ca²⁺ oscillations and enhances

insulin release; the TRPM3 antagonist isosakuranetin inhibited these responses. In conclusion, we established a cost-effective and scalable 3D -cell platform for high-throughput screening of insulin release-modifying compounds, with potential applications in drug development and personalized medicine for the management of diabetes mellitus.

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- HELD, K., VAN HOEYMISSEN, E., DALLALI, I., PERSOONS, E., BAZELI, B., ROELEN, S., ROBBER, S., WUYTS, C., MULIER, M., PINTO, S., JANSSENS, A., **VOETS, T.** & VRIENS, J.
A duo of redox-sensitive pore-loop cysteines controls the activity of the neural ion channel TRPM3.

Commun Chem (in press) 2025

Commun Chem: 2026 Jan 14;9(1):86. doi: 10.1038/s42004-026-01889-9.

Affiliations Expand

PMID: 41530372 - PMCID: PMC12905292 - DOI: 10.1038/s42004-026-01889-9

Abstract

Transient Receptor Potential Melastatin 3 (TRPM3) is a non-selective, Ca²⁺-permeable ion channel that plays a pivotal role in peripheral thermosensation and nociception. Moreover, gain-of-function variants in TRPM3 underlie a spectrum of neurodevelopmental and epileptic disorders in humans, indicating an important role of TRPM3 in the central nervous system. Oxidative stress contributes to various neurological disorders of both the central and peripheral nervous system, but it is unknown whether TRPM3 activity is altered by the cellular redox state. Here, we report a direct, bidirectional modification of TRPM3 channel activity by oxidizing and reducing agents. Our data demonstrate a profound effect of the redox state on the channel properties of TRPM3, including a robust shift in the response profile to pharmacology and temperature sensitivity. In addition, we identified two cysteine residues in the extracellular pore loop of TRPM3 that underlie the redox-control of the channel, due to the reversible formation of intra-subunit cysteine bridges. Taken together, these observations raise the hypothesis that TRPM3 could be modulated through an alternative mechanism, potentially affecting pathways involved in pain and neurological function.

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Faculté de Médecine

Département des sciences cliniques

Neurologie

GIGA CRC In vivo Imaging – Sleep and chronobiology

Bât. B35 Neurologie

Quartier Hôpital

avenue de l'Hôpital 13, 4000 Liège 1, Belgique

Téléphone de service: +32 4 366 23 67

Téléphone de service: +32 4 366 23 62

Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- No publications in 2023

Publications in 2024 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- No publications in 2024

Publications in 2025 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

An abstract of the project has been accepted by the Belgium Stroke Council, and the project has been presented at the 8th Belgian Scientific Stroke Workshop on October 17th, 2025. We have been selected to also present our project at the Belgium Stroke Council symposium on December 13th, 2025.



Geneeskundige Stichting Koningin Elisabeth
Fondation Médicale Reine Elisabeth
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2023–2025 gefinancierd door de G.S.K.E.

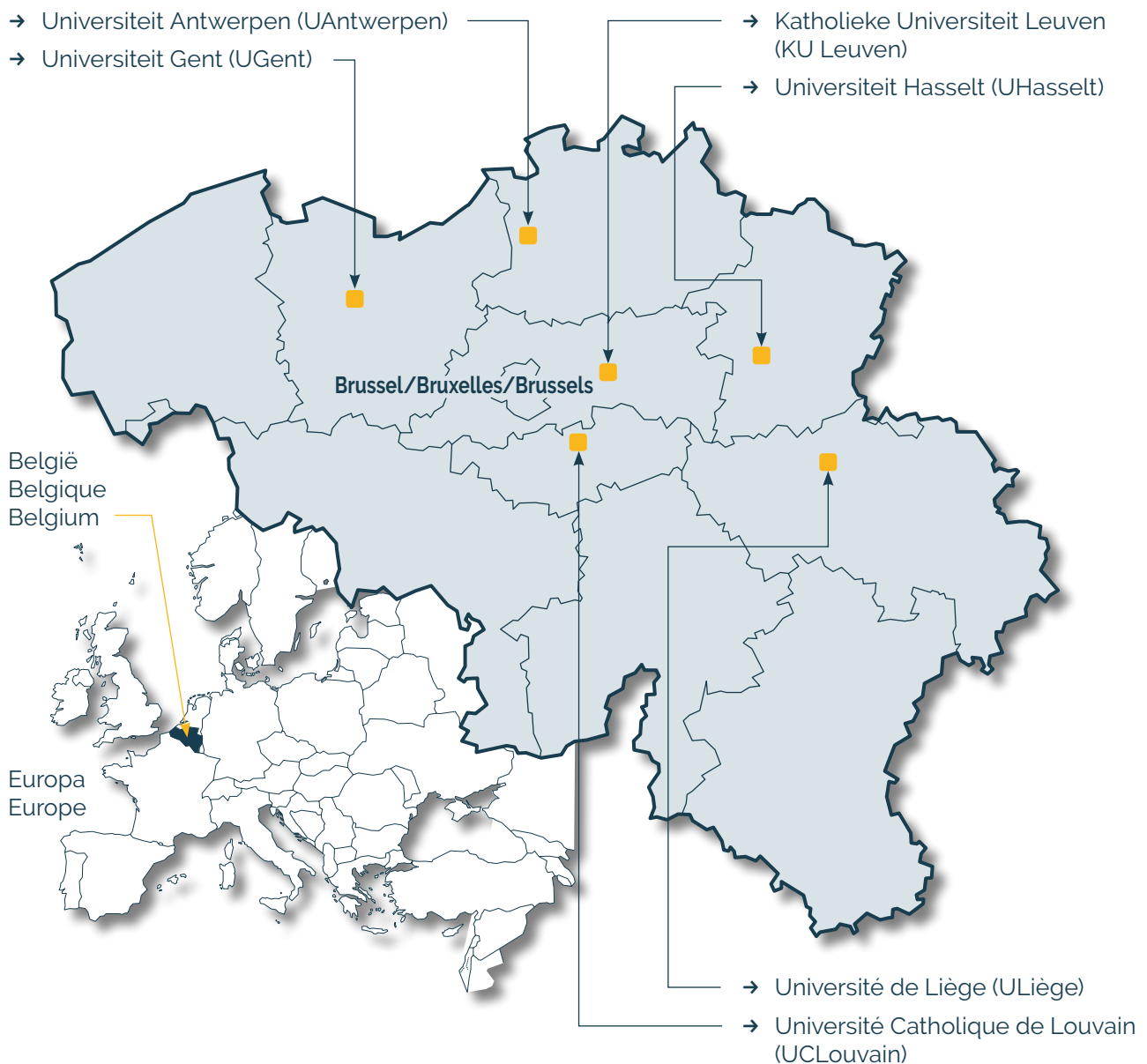
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Projecten jonge onderzoekers 2023-2025 gefinancierd door de G.S.K.E.

Projets de recherche de jeunes chercheurs 2023-2025 subventionnés par la F.M.R.E.

Research projects of young researchers 2023-2025 funded by the Q.E.M.F.

UGent



Sielke Caestecker (PhD student) & promotor prof. Robrecht Raedt

The role of the locus coeruleus noradrenergic system in seizures and epilepsy

Dr. Delfien Syx

Zebrafish as a model to study pain in Ehlers-Danlos syndromes

UAntwerpen



Dr. Marijne Vandebergh

World-wide systematic characterization of TMEM106B and ATXN2 genetic status Towards implementation of genetic testing of modifiers in clinical practice

Dr. Barbara M.P. Willekens

Unravelling the role of antigen-specific T cells in NMOSD and MOGAD

KU Leuven



Dr. Wouter Peelaerts

Peripheral infections as a trigger of multiple system atrophy

Dr. Sarah van Veen

The impact of ATP13A4-mediated polyamine transport in astrocytes on synaptogenesis and neurodevelopmental disorders

UCLouvain



Prof. Giulia Liberati

STIM-WAVES: Identifying pain biomarkers with invasive and non-invasive brain stimulation targeting ongoing neural oscillations

(UHasselt)



Prof. dr. Jeroen Bogie

Getting a grip on slippery protein modifications in multiple sclerosis

Prof. dr. Bieke Broux

High salt diet causes blood-brain barrier disturbances in multiple sclerosis: involvement of the renin-angiotensin-aldosterone system

ULiège



Dr. Sophie Laguesse

Unveiling the alcohol-dependent alterations in mRNA local translation and its consequences on adolescent prefrontal cortex maturation and function



Geneeskundige Stichting Koningin Elisabeth
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Publicaties – Publications –
Publikationen – Publications

UGent

Prof. dr. Robrecht Raedt & PhD Sielke Caestecker

Prof. dr. Robrecht Raedt (UGent)

Principal investigator – 4BRAIN

Associate Professor (Faculty of Medicine and Health Sciences)

Director of the Animal Facility of the Faculty of Medicine and Health Sciences

Member of GATE steering committee

Secretary of the Belgian Society for Neuroscience

Lab address: 4BRAIN,

Campus UZ Gent, o Blok B (entrance 36),

Corneel Heymanslaan 10,

9000 Gent, Belgium

Robrecht.Raedt@UGent.be

Sielke Caestecker (UGent)

PhD student

Lab address: 4BRAIN,

Campus UZ Gent, o Blok B (entrance 36), Corneel Heymanslaan 10,

9000 Gent, Belgium

sielke.caestecker@ugent.be

Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- LARS EMIL LARSEN · SIELKE CAESTECKER · LATOYA STEVENS · PIETER VAN MIERLO · EVELIEN CARRETTE · PAUL BOON · KRISTL VONCK · ROBRECHT RAEDT

Hippocampal seizures differentially modulate locus coeruleus activity and result in consistent time-locked release of noradrenaline in rat hippocampus

Neurobiol Dis, 2023 Dec;189:106355., doi: 10.1016/j.nbd.2023.106355. Epub 2023 Nov 15.

Abstract

The locus coeruleus (LC) is a small brainstem nucleus and is the sole source of noradrenaline in the neocortex, hippocampus and cerebellum. Noradrenaline is a powerful neuromodulator involved in the regulation of excitability and plasticity of large-scale brain networks. In this study, we performed a detailed assessment of the activity of locus coeruleus neurons and changes in noradrenergic transmission during acute hippocampal seizures evoked with perforant path stimulation, using state-of-the-art methodology. Action potentials of LC neurons, of which some were identified by means of optogenetics, were recorded in anesthetized rats using a multichannel high-density electrophysiology probe. The seizure-induced change in firing rate differed between LC neurons: 55% of neurons decreased in firing rate during seizures, while 28% increased their firing rate. Topographic analysis of multi-unit activity over the electrophysiology probe showed a topographic clustering of neurons that were inhibited or excited during seizures. Changes in hippocampal noradrenaline transmission during seizures were assessed using a fluorescent biosensor for noradrenaline, GRAB_{NE2m}, in combination with fiber photometry, in both anesthetized and awake rats. Although our neuronal recordings indicated both inhibition and excitation of LC neurons during seizures, a consistent release of noradrenaline was observed. Concentrations of noradrenaline increased at seizure onset and decreased during or shortly after the seizure. In conclusion, this study showed consistent but heterogeneous modulation of LC neurons and a consistent time-locked release of hippocampal noradrenaline during acute hippocampal seizures.

Keywords: Epilepsy; Locus coeruleus; Noradrenaline; Optogenetics; Photometry; Seizure.

Funding

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Publications in 2024 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- SIELKE CAESTECKER, EMMA LESCRAUWAET, KRISTL VONCK, MATHIEU SPRENGERS, EVELIEN CARRETTE, PAUL BOON, LARS EMIL LARSEN, ROBRECHT RAEDT
Chemogenetic modulation of the rat locus coeruleus alters hippocampal noradrenaline release and modulates perforant path-evoked responses
Frontiers in Neuroscience – Translational Neuroscience IF : 3.2 (2023) Q factor : Q2

Abstract

The locus coeruleus (LC)—noradrenaline (NA) system plays a crucial role in modulating neuronal excitability and plasticity. In epilepsy, the LC-NA system plays an important role in regulating seizure thresholds and severity, with elevated NA release mediating the seizure-suppressing effects of vagus nerve stimulation (VNS). We investigated whether chemogenetic LC activation is able to increase hippocampal NA release and affect hippocampal electrophysiology in anesthetized rats.

Methods: 22 male Sprague—Dawley rats were injected with the viral vector AAV9-hSyn-NE2m in the hippocampus to induce expression of the GRABNE2m biosensor to locally measure changes in extracellular NA. 15/22 rats were injected with the CAV2-PRsx8-hM3Dq hSyn-mCherry viral vector in the LC to express the excitatory DREADD hM3Dq, allowing LC activation with deschloroclozapine (DCZ), and 7/22 with CAV2-PRsx8-GtACR2 as a control. A perforant path stimulation electrode and a dentate gyrus (DG) recording electrode were implanted for local field potential (LFP) and evoked potential (EP) recording as well as a DG optical fiber for GRABNE2m fluorescence measurement.

Results: In a significant number of rats (7/15) we found an increase in hippocampal NA release, field excitatory post synaptic potential (fEPSP) slope and population spike (PS) amplitude, indicating an increase in excitatory neurotransmission and neuronal output. 4/15 rats showed a decrease in NA release without changes in fEPSP slope or PS amplitude, and 4/15 showed no change in NA release.

Discussion: These findings indicate that chemogenetic activation of the LCNA system can modulate hippocampal evoked responses, supporting further exploration of its role in health and disease, such as in epilepsy.

Keywords locus coeruleus (LC), noradrenaline (NA), chemogenetics, GRABNE2m biosensor, hippocampus (HC), evoked potentials (EPs), epilepsy Frontiers in Neuroscience 01 frontiersin.org

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Publications in 2025 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- No publications in 2025

Dr. Delfien Syx

Department of Biomolecular Medicine
Center for Medical Genetics Ghent (CMGG)
Ghent University Hospital
Medical Research Building I (MRB I) – Ingang 34
C. Heymanslaan 10
B-9000 Ghent
Belgium
T +32 9 33 2 1346
Delfien.Syx@ugent.be
www.cmgg.be
www.ugent.be/ge/biomolecular-medicine

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Königin-Elisabeth-Stiftung für Medizin
Queen Elisabeth Medical Foundation

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UAntwerpen

Dr. Marijne Vandenberg (UAntwerpen)

Campus Drie Eiken Center for Molecular Neurology

Universiteitsplein 1 2610 Wilrijk marijne.vandebergh@uantwerpen.be

Tel. +3232653978

Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

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Publications in 2024 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- MARIJNE VANDEBERGH, ELIANA MARISA RAMOS, NICK CORRIVEAU-LECAVALIER, VIJAY K. RAMANAN, JOHN KORNAK, CARLY MESTER, TYLER KOLANDER, DANIELLE E. BRUSHABER, ADAM M. STAFFARONI, DANIEL H. GESCHWIND, AMY A. WOLF, KEJAL KANTARCI, TANIA GENDRON, LEONARD PETRUCCELLI, MARLEEN VAN DEN BROECK, SARAH WYNANTS, MATTHEW BAKER, SERGI BORREGO-ÉCIJA, BRIAN APPLEBY, SAMI BARMADA, ANDREA C. BOZOKI, DAVID CLARK, R. RYAN DARBY, BRADFORD C. DICKERSON, KIMIKO DOMOTO-REILLY, JULIE A. FIELDS, DOUGLAS GALASKO, NUPUR GHOSHAL, NEILL R. GRAFF-RADFORD, IAN M. GRANT, LAWRENCE S. HONIG, GING-YUEK R. HSIUNG, EDWARD D. HUEY, DAVID J. IRWIN, DAVID S. KNOPMAN, JUSTIN Y. KWAN, GABRIEL C. LÉGER, IRENE LITVAN, JOSEPH C. MASDEU, MARIO F. MENDEZ, CHIADI U. ONYIKE, BELEN PASCUAL, PETER S. PRESSMAN, AARON RITTER, ERIK D. ROBERSON, ALLISON SNYDER, ANNA CAMPBELL SULLIVAN, MARIA CARMELA TARTAGLIA, DYLAN WINT, ROSA RADEMAKERS, ALLFTD CONSORTIUM.

Volume and Cognition of TMEM106B in Frontotemporal Lobar Degeneration

Accepted for publication: August 19, 2024

Neurology Impact factor: 8.4 Q factor: Q1

Abstract

Background and Objectives: TMEM106B has been proposed as a modifier of disease risk in FTLD-TDP, particularly in GRN pathogenic variant carriers. Furthermore, TMEM106B has been investigated as a disease modifier in the context of healthy aging and across multiple neurodegenerative diseases. The objective of this study was to evaluate and compare the effect of TMEM106B on gray matter volume and cognition in each of the common genetic FTD groups and in patients with sporadic FTD.

Methods: Participants were enrolled through the ARTFL/LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) study, which includes symptomatic and presymptomatic individuals with a pathogenic variant in C9orf72, GRN, MAPT, VCP, TBK1, TARDBP, symptomatic nonpathogenic variant carriers, and noncarrier family controls. All participants were genotyped for the TMEM106B rs1990622 SNP. Cross-sectionally, linear mixed-effects models were fitted to assess an association between TMEM106B and genetic group interaction with each outcome measure (gray matter volume and UDS3-EF for cognition), adjusting for education, age, sex, and CDR+NACC-FTLD sum of boxes. Subsequently, associations between TMEM106B and each outcome measure were investigated within the genetic group. For longitudinal modeling, linear mixed-effects models with time by TMEM106B predictor interactions were fitted.

Results:

The minor allele of TMEM106B rs1990622, linked to a decreased risk of FTD, associated with greater gray matter volume in GRN pathogenic variant carriers under the recessive dosage

model (N = 82, beta = 3.25, 95% CI [0.37–6.19], p = 0.034). This was most pronounced in the thalamus in the left hemisphere (beta = 0.03, 95% CI [0.01–0.06], p = 0.006), with a retained association when considering presymptomatic GRN pathogenic variant carriers only (N = 42, beta = 0.03, 95% CI [0.01–0.05], p = 0.003). The minor allele of TMEM106B rs1990622 also associated with greater cognitive scores among all C9orf72 pathogenic variant carriers (N = 229, beta = 0.36, 95% CI [0.05–0.66], p = 0.021) and in presymptomatic C9orf72 pathogenic variant carriers (N = 106, beta = 0.33, 95% CI [0.03–0.63], p = 0.036), under the recessive dosage model.

Discussion: We identified associations of TMEM106B with gray matter volume and cognition in the presence of GRN and C9orf72 pathogenic variants. The association of TMEM106B with outcomes of interest in presymptomatic GRN and C9orf72 pathogenic variant carriers could additionally reflect TMEM106B's effect on divergent pathophysiologic changes before the appearance of clinical symptoms

Disclosure: M. Vandebergh received funding for this project from the Queen Elisabeth Medical Foundation of Neurosciences (GSKE).

Publications in 2025 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- MARIJNE VANDEBERGH, ELIANA MARISA RAMOS, DANIEL GESCHWIND, SAIRA MIRZA, MARIO MASELLIS, EKATERINA ROGAEVA, LUCY CHISMAN-RUSSELL, JONATHAN ROHRER, HILARY HEUER, LEAH FORSBERG, ADAM BOXER, HOWARD ROSEN, BRADLEY BOEVE, AND ROSA RADEMAKERS

The road towards implementation of TMEM106B genetic testing in clinical practice in progranulin pathogenic variant carriers

Published: April 7, 2025 **Journal: Neurology** (online) Impact factor: 9 Q factor: Q1 doi: <https://doi.org/10.1212/WNL.0000000000210476>

Abstract

Objective: Through characterization of the *TMEM106B* haplotype in large well-characterized cohorts of *GRN* pathogenic variant carriers, we aim to provide support for implementation of *TMEM106B* genetic testing in *GRN* pathogenic variant carriers in clinical testing.

Background: Clinical genetic testing has been focused on autosomal dominant risk-increasing mutations rather than on genetic modifiers of disease. While *TMEM106B* has been shown to modify disease penetrance in *GRN* pathogenic variant carriers, genotyping of *TMEM106B* in *GRN* pathogenic variant carriers is currently not conducted in a clinical setting, not even in the event of a positive genetic test result for *GRN* in an asymptomatic individual.

Design/Methods: Systematic genotype screens for *TMEM106B* haplotype in well-characterized cohorts, including cohorts from the ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) consortium and the Genetic FTD Initiative (GENFI), are conducted.

Results: Our preliminary data indicate a lower proportion of individuals homozygous for the protective *TMEM106B* haplotype in *GRN* carriers compared to individuals with a *C9orf72* repeat expansion, *MAPT* pathogenic variant or non-mutation carriers. The majority of *GRN* carriers homozygous for the protective *TMEM106B* haplotype are asymptomatic. Importantly, some are still healthy despite relatively old age (> 70y). In those that are symptomatic, we have identified a case with a *CSF1R* mutation on top of the *GRN* mutation with a Parkinson-like phenotype. Whole genome sequencing is currently ongoing to further investigate other genetic causes

of disease in symptomatic *GRN* carriers homozygous for the protective *TMEM106B* haplotype. **Conclusions:** Through investigation of *TMEM106B* haplotypes in *GRN* carriers we show that individuals with a *GRN* variant and homozygous for the protective haplotype are still healthy despite relatively old age, and that the disease in those affected might be caused by other genetic factors. Screening for *TMEM106B* in a clinical setting has important implications for genetic counselling and clinical trial inclusion criteria for *GRN* carriers.

Funding

Dr. Vandebergh has received research support from the **Queen Elisabeth Medical Foundation** for Neurosciences.

Dr. Barbara M.P. Willekens

Neurologist | MS & CNS Neuroimmune Disorders

T +32 3 821 34 23

Barbara.willekens@uza.be

Department of Neurology

UZA, Drie Eikenstraat 655, 2650 Edegem

T +32 3 821 30 00

www.uza.be/neurologie

University of Antwerp

Translational Neurosciences Research Group

Laboratory of Experimental Hematology, Vaccine & Infectious Disease Institute
(VAXINFECTIO)

Faculty of Medicine and Health Sciences

Universiteitsplein 1, 2610 Antwerp, Belgium

Barbara.willekens@uantwerpen.be

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KU Leuven

Dr. Wouter Peelaerts (KU Leuven)

Department of Neurosciences

Laboratory for Neurobiology and Gene Therapy

Department of Pharmacy and pharmaceutical

O&N5b-Herestraat 49 box 1023 – 3000 Leuven, belgium

Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- WOUTER PEELAERTS, GABRIELA MERCADO, SONIA GEORGE, MARIE VILLUMSEN, ALYSA KASEN, MIGUEL AGUILETA, CHRISTIAN LINSTOW, ALEXANDRA B SUTTER, EMILY KUHN, LUCAS STETZIK, RACHEL SHERIDAN, LIZA BERGKVIST, LINDSAY MEYERDIRK, ALLISON LINDQVIST, MARTHA L ESCOBAR GAVIS, CHRIS VAN DEN HAUTE, SCOTT J HULTGREN, VEERLE BAEKELANDT, J ANDREW POSPISILIK, TOMASZ BRUDEK, SUSANA AZNAR, JENNIFER A STEINER, MICHAEL X HENDERSON, LENA BRUNDIN, MAGDALENA I IVANOVA, TOM J HANNAN, PATRIK BRUNDIN

Urinary tract infections trigger synucleinopathy via the innate immune response.

Acta Neuropathol. 2023

May;145(5):541-559., doi: 10.1007/s00401-023-02562-4. Epub 2023 Mar 30.

PMID: 36991261, PMCID: PMC10119259, DOI: 10.1007/s00401-023-02562-4

Abstract

Symptoms in the urogenital organs are common in multiple system atrophy (MSA), also in the years preceding the MSA diagnosis. It is unknown how MSA is triggered and these observations in prodromal MSA led us to hypothesize that synucleinopathy could be triggered by infection of the genitourinary tract causing α -synuclein (Syn) to aggregate in peripheral nerves innervating these organs. As a first proof that peripheral infections could act as a trigger in MSA, this study focused on lower urinary tract infections (UTIs), given the relevance and high frequency of UTIs in prodromal MSA, although other types of infection might also be important triggers of MSA. We performed an epidemiological nested-case control study in the Danish population showing that UTIs are associated with future diagnosis of MSA several years after infection and that it impacts risk in both men and women. Bacterial infection of the urinary bladder triggers synucleinopathy in mice and we propose a novel role of Syn in the innate immune system response to bacteria. Urinary tract infection with uropathogenic *E. coli* results in the de novo aggregation of Syn during neutrophil infiltration. During the infection, Syn is released extracellularly from neutrophils as part of their extracellular traps. Injection of MSA aggregates into the urinary bladder leads to motor deficits and propagation of Syn pathology to the central nervous system in mice overexpressing oligodendroglial Syn. Repeated UTIs lead to progressive development of synucleinopathy with oligodendroglial involvement in vivo. Our results link bacterial infections with synucleinopathy and show that a host response to environmental triggers can result in Syn pathology that bears semblance to MSA.

Acknowledgments

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- No publications in 2024

Publications in 2025 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- BARBER-JANER A, VAN ACKER E, VONCK E, PLESSERS D, ROSADA F, VAN DEN HAUTE C, BAEKELANDT V, **PEELAERTS W.**

Development of convolutional neural networks for automated brain-wide histopathological analysis in mouse models of synucleinopathies.

npj Parkinson's Disease. 2025;11:317. DOI: 10.1038/s41531-025-01170-1.

Impact Factor: 8.2 – Q1

Abstract

Preclinical animal models are indispensable for uncovering disease mechanisms and developing novel therapeutic interventions in synucleinopathies. Key readouts including neuronal cell death, neuroinflammation and alpha-synuclein protein aggregation, are routinely assessed by histological methods. However, traditional characterization of histological samples is labor-intensive and time-consuming. There is a growing need for reproducible and high-throughput tools to capture region- and cell type-specific changes, ultimately improving the predictive value of preclinical studies. To address this, our study introduces a pipeline using convolutional neural networks (CNNs) for high-throughput, unbiased analysis of immunohistological data in mouse brains. We have trained five CNN-based models to autonomously identify brain regions and detect markers of neurodegeneration, neuroinflammation, and alpha-synuclein aggregation. These models provide accurate, region-specific insights at cellular resolution without manual annotation, significantly speeding up analysis time from weeks to minutes. Our approach enhances the precision and efficiency of histological assessments, providing robust, brain-wide results in various animal models of synucleinopathies.

Acknowledgments

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Dr. Sarah van Veen, PhD (KU Leuven)

FWO postdoctoral fellow

Laboratory of Cellular Transport Systems

KU Leuven, Department of Cellular and Molecular Medicine

ON Ibis Herestraat 49, box 802 – 3000 Leuven (Belgium)

T +32 (0)16 32 90 55

sarah.vanveen@kuleuven.be

Publications in 2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- VAN VEEN S., IRALA D., HAYS K., AUSLOOS E., VAN ASSELBERGHS J., VAN DEN HAUTE C., BAEKELANDT V., EGGERMONT J., HOLT M.G., EROGLU C., VANGHELUWE P.
Connecting polyamine transport in astrocytes to neurodevelopmental disorders via TP13A4. Manuscript in preparation.

Abstract

During my FWO PhD fellowship, I proved that ATP13A2 works as a lysosomal polyamine exporter implicated in neurodegenerative disorders. Here, I will focus on a closely related isoform, ATP13A4, which is genetically associated with neurodevelopmental disorders. ATP13A4 is localized predominantly in astrocytes and according to my preliminary data may also function as a polyamine transporter. Polyamines are regulators of astrocyte functionality and neuronal modulation, but how polyamines are taken up by astrocytes remains unknown. I therefore hypothesize that ATP13A4 may mediate polyamine uptake in astrocytes, whereas ATP13A4 dysfunction may disturb polyamine homeostasis, ultimately leading to astrocyte and/or neuronal dysfunction underlying neurodevelopmental disorders. To test this hypothesis, I will use complementary biochemical and cellular assays to characterize the molecular properties of ATP13A4 wildtype and disease mutants. I will further assess the impact of Atp13a4 deficiency on astrocyte polyamine homeostasis, endosomal functionality and relevant astrocyte functions. To analyse the in vivo consequences of Atp13a4 deficiency, an astrocyte-specific Atp13a4 knock-out mouse strain will be generated to determine the impact of Atp13a4 on astrocyte/neuronal interplay and mouse behaviour. Understanding the physiological role of ATP13A4 in astrocytes and in the brain may validate ATP13A4 as a candidate therapeutic target for neurodevelopmental disorders.

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- No publications in 2024

Publications in 2025 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- **VAN VEEN S.**, IRALA D., SAKERS K., SAVAGE J., SÉJOURNÉ G., SIVADASAN BINDU D., AUSLOOS E., DHONDT H., SCHOONVLIET N., VAN DEN HAUTE C., VAN ASSELBERGHS J., WIERDA K., BAEKELANDT V., PLATZER K., ROSTASY K., YAP KL., EGGERMONT J., HOLT M., EROGLU C., VANGHELUWE P.
Astrocytic polyamine transport by ATP13A4 tunes excitatory synaptic transmission. Preprint at medRxiv (2025).
DOI: 10.1101/2025.04.04.25325117.

Abstract

Polyamines, such as spermidine and spermine, are essential for brain function and neurodevelopment. These soluble molecules modulate glial and neuronal ion channels, transporters, and receptors, contributing to cellular communication in the brain. Within the brain, polyamines primarily accumulate in astrocytes, but the mechanisms of polyamine uptake in astrocytes and the physiological relevance of this process in brain function remain poorly understood. Here, we identified ATP13A4, a P5B-type transport ATPase predominantly expressed in astrocytes, as a key polyamine transporter that regulates polyamine uptake and homeostasis in astrocytes. Using primary cultures and rodent models, we show that ATP13A4 deficiency reduces astrocyte morphological complexity and increases excitatory synapse formation. Exogenous spermidine application recapitulated these effects, suggesting that astrocytes play a critical role in clearing extracellular polyamines. Moreover, we identified a novel homozygous p.E276K variant of ATP13A4 in a patient with intellectual disability and a heterozygous deletion spanning exons 19-25 in a patient with epilepsy. Additionally, we characterized two ATP13A4 variants previously associated with autism and language impairment. These variants exhibited loss-of-function phenotypes, pointing to a link between imbalanced polyamine homeostasis and neurodevelopmental disorders. Correspondingly, *Atp13a4* KO mice exhibit mild, sex-specific behavioral deficits. Female KO mice display subtle changes in anxiety-like behavior, spatial learning, motor coordination, and seizure susceptibility, aligning with features observed in patients with loss-of-function ATP13A4 mutations. In summary, astrocytes take up extracellular polyamines via ATP13A4, which regulate astrocyte arborization and excitatory synapse formation, significantly impacting neurodevelopment and behavior. This work provides the first direct link between dysfunctional astrocytic polyamine transport and perturbations in brain development, providing novel insights into the molecular mechanisms underlying neurodevelopmental disorders.

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UCLouvain

Prof. Giulia Liberati (UCLouvain)

Université catholique de Louvain Institute of Neuroscience (IoNS)

Avenue Mounier 54

UCL 54.02 B-1200 Brussels

Belgium

T +32 (2) 7645467

giulia.liberati@uclouvain.be

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- CHIARI LEU, ESTHER GLINEUR and GIULIA LIBERATI

Cue-based modulation of pain stimulus expectation: do ongoing oscillations reflect changes in pain perception? A registered report

R Soc Open Sci 2024 Jun 19;11(6):240626. doi: 10.1098/rsos.240626. eCollection 2024 Jun

Abstract

A promising stream of investigations is targeting ongoing neural oscillations and whether their modulation could be related to the perception of pain. Using an electroencephalography (EEG) frequency-tagging approach, sustained periodic thermonociceptive stimuli perceived as painful have been shown to modulate ongoing oscillations in the theta, alpha and beta bands at the frequency of stimulation. Nonetheless, it remains uncertain whether these modulations are indeed linked to pain perception. To test this relationship, we modulated pain perception using a cue-based expectation modulation paradigm and investigated whether ongoing oscillations in different frequency bands mirror the changes in stimulus perception. Forty healthy participants were instructed that a visual cue can precede either a high- or low-intensity stimulation. These cues were paired with three different levels of sustained periodic thermonociceptive stimuli (low, medium and high). Despite a strong effect of expectation on perceived stimulus intensity, this effect was not reflected in the modulation of the ongoing oscillations, suggesting a potential dissociation of pain perception and these oscillatory activities. Rather, it seems that the intensity of stimulation is the primary generator of the frequency-tagged EEG responses. Importantly, these results need to be confirmed by further investigations that could allow the detection of smaller effects than originally estimated.

Keywords: expectation; frequency-tagging; neural oscillations; nociception; pain.

Funding

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Publications in 2025 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- GIULIA LIBERATI: PRINCIPAL INVESTIGATOR (UCLouvain) - CHIARA LEU: PHD STUDENT (UCLouvain) - SEBASTIEN FOREST: MASTER STUDENT AND INTERN (UCLouvain)

The effect of stimulus saliency on the modulation of ongoing neural oscillations related to thermonociception (complete)

Cortex 2025 Apr;185:316-335. doi: 10.1016/j.cortex.2025.02.009. Epub 2025 Mar 5.

Abstract

Ongoing oscillations have been shown to be modulated in different frequency bands following phasic, tonic as well as periodic thermonociceptive stimulation. Yet, it remains unclear whether these modulations are related to pain perception, saliency (i.e., the ability of a stimulus to stand out from its environment) or solely the intensity of these stimuli. Thirty-five participants were recruited to investigate the relationship between pain perception and ongoing oscillations as well as the factors likely to modulate them, combining a sustained periodic thermonociceptive stimulation paradigm including periodic oddball events with a frequency-tagging analysis approach. Oddballs were delivered either at a higher or lower intensity ("high oddball" versus "low oddball" condition) than baseline stimuli. Continuous ratings of pain perception were collected during the stimulation to track participants' perception. Despite the stimuli being barely perceived as painful (hence relating predominantly to thermonociception), the continuous ratings of perception clearly reflected the variations of stimulus intensity, but only in the "high oddball" condition. Consistently, the oddball stimulus modulated ongoing oscillations in the "high oddball", but not in the "low oddball" condition. Because of the lack of differentiation between baseline and oddball cycles in the "low oddball" condition - both in perception and at the neural level - these findings do not allow disentangling the differential effects of stimulus intensity and saliency on the perception of thermonociceptive stimuli, or on the modulation of oscillatory activities related to thermonociception. However, they indicate the modulation of ongoing oscillations reflects subjects' perception of thermonociceptive stimuli that are both salient and intense.

Keywords: EEG; Frequency tagging; Nociception; Ongoing oscillations; Pain; Saliency.

Acknowledgments

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- GIULIA LIBERATI: PRINCIPAL INVESTIGATOR (UCLouvain) - CHIARA LEU: PHD STUDENT (UCLouvain) - AÏCHA BOUTACHKOURT: PHD STUDENT (UCLouvain)

The effect of attention on pain-related oscillations recorded from the human insula using intracerebral EEG (complete)

- GIULIA LIBERATI: PRINCIPAL INVESTIGATOR (UCLouvain) - YASER FATHI ARATEH: POSTDOCTORAL RESEARCHER (UCLouvain) - FRANÇOISE DISSASSUCA: MASTER STUDENT AND INTERN (UCLouvain) - GLORIA RICCI: ERASMUS MASTER STUDENT AND INTERN (UNIVERSITÀ DI PADOVA)

Individualized alpha-transcranial alternating current stimulation (tACS) for modulating pain perception (complete)

Eur J Pain: 2025 Aug;29(7):e70086. doi: 10.1002/ejp.70086.

Abstract

Background: Neural oscillations are increasingly recognised as key mechanisms integrating the sensory, affective and cognitive dimensions of pain, yet their precise role in pain modulation remains poorly understood. Transcranial alternating current stimulation (tACS) offers a promising tool for modulating these oscillations and elucidating their function in pain processing. However, findings on tACS-induced pain modulation have been inconsistent, possibly due to a lack of individualised protocols.

Methods: In this study, we investigated the effects of tACS delivered at the individual peak alpha frequency (IAF) on both pain perception and neural oscillations. Using a within-subject, sham-controlled design, we applied tACS over the primary motor cortex (M1) contralateral to the dominant arm in 38 healthy participants. Sustained periodic 0.2 Hz thermosensory stimuli were applied to the dominant forearm before and after tACS. Pain perception and heat pain thresholds (HPT) were assessed before and after tACS. To calculate IAF from recorded scalp electroencephalography, we used a discriminative approach based on independent component analysis, enabling the isolation of somatosensory IAF (SS-IAF).

Results: The results revealed an overall increase in pain perception and a decrease in HPT in both sham and active conditions, with no significant interactions between conditions. However, a trend toward reduced sensitisation to thermosensory stimuli post-tACS was observed. Exploratory analyses suggested a sex-specific effect of tACS, with a potential modulation of HPT observed in women but not in men. Furthermore, we observed a significant correlation between SS-IAF and HPT.

Conclusions: These findings provide novel perspectives on advancing individualised neuromodulation approaches for pain.

Significance: This article introduces an individualised transcranial alternating current stimulation (tACS) approach, targeting the sensorimotor area at the individual somatosensory alpha frequency. Our findings highlight its potential for modulating pain perception and provide novel perspectives on advancing individualised neuromodulation for pain management.

Keywords: individual alpha frequency (IAF); neural oscillations; nociception; pain perception; transcranial alternating current stimulation (tACS).

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- GIULIA LIBERATI: PRINCIPAL INVESTIGATOR (UCLOUVAIN) - YASER FATHI ARATEH: POSTDOCTORAL RESEARCHER (UCLOUVAIN) - FRANÇOISE DISSASSUCA: MASTER STUDENT AND INTERN (UCLOUVAIN) - GLORIA RICCI: ERASMUS MASTER STUDENT AND INTERN (UNIVERSITÀ DI PADOVA)

Individualized alpha-transcranial alternating current stimulation (tACS) for modulating pain perception and Neural Oscillations: A Sham-Controlled Study in Healthy Participants

Eur J Pain: 2025 Aug;29(7):e70086. doi: 10.1002/ejp.70086.

Abstract

Background: Neural oscillations are increasingly recognised as key mechanisms integrating the sensory, affective and cognitive dimensions of pain, yet their precise role in pain modulation remains poorly understood. Transcranial alternating current stimulation (tACS) offers a promising

tool for modulating these oscillations and elucidating their function in pain processing. However, findings on tACS-induced pain modulation have been inconsistent, possibly due to a lack of individualised protocols.

Methods: In this study, we investigated the effects of tACS delivered at the individual peak alpha frequency (IAF) on both pain perception and neural oscillations. Using a within-subject, sham-controlled design, we applied tACS over the primary motor cortex (M1) contralateral to the dominant arm in 38 healthy participants. Sustained periodic 0.2 Hz thermonociceptive stimuli were applied to the dominant forearm before and after tACS. Pain perception and heat pain thresholds (HPT) were assessed before and after tACS. To calculate IAF from recorded scalp electroencephalography, we used a discriminative approach based on independent component analysis, enabling the isolation of somatosensory IAF (SS-IAF).

Results: The results revealed an overall increase in pain perception and a decrease in HPT in both sham and active conditions, with no significant interactions between conditions. However, a trend toward reduced sensitisation to thermonociceptive stimuli post-tACS was observed. Exploratory analyses suggested a sex-specific effect of tACS, with a potential modulation of HPT observed in women but not in men. Furthermore, we observed a significant correlation between SS-IAF and HPT.

Conclusions: These findings provide novel perspectives on advancing individualised neuromodulation approaches for pain.

Significance: This article introduces an individualised transcranial alternating current stimulation (tACS) approach, targeting the sensorimotor area at the individual somatosensory alpha frequency. Our findings highlight its potential for modulating pain perception and provide novel perspectives on advancing individualised neuromodulation for pain management.

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- GIULIA LIBERATI: PRINCIPAL INVESTIGATOR (UCLouvain) - GLORIA RICCI: ERASMUS MASTER STUDENT AND INTERN (UNIVERSITÀ DI PADOVA) - YASER FATHI ARATEH: POSTDOCTORAL RESEARCHER (UCLouvain)

Using periodic oscillations to analyze tACS effects on IAF (in progress)

- GIULIA LIBERATI: PRINCIPAL INVESTIGATOR (UCLouvain) - YASER FATHI ARATEH: POSTDOCTORAL RESEARCHER (UCLouvain)

Precision targeting of temporal interference stimulation (TIS) over the insula using computational modeling and cadaver investigations (complete)

- GIULIA LIBERATI: PRINCIPAL INVESTIGATOR (UCLouvain) - CHIARA LEU: PHD STUDENT (UCLouvain) - ANDRÉ MOURAUX (UCLouvain) - PAOLO BELARDINELLI: EXTERNAL COLLABORATOR (UNIVERSITY OF TRENTO)

Exploring the link between ongoing oscillations and pain perception through highfrequency rTMS: a brain-state dependent TMS-EEG study (in progress)

- GIULIA LIBERATI: PRINCIPAL INVESTIGATOR (UCLouvain) - JAVIER CHAVEZ CERDA: POSTDOCTORAL RESEARCHER (UCLouvain)

Exploring the effects of transcutaneous auricular vagus nerve stimulation (taVNS) on pain perception (in progress)



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Publicaties – Publications –
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UHasselt

Prof. dr. Jeroen Bogie (UHasselt)

Assistant Professor

T +32(0)11 26 92 61

www.uhasselt.be

Universiteit Hasselt – Campus Diepenbeek

Agoralaan Gebouw D – B-3590 Diepenbeek

Kantoor BMO-C107a

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- KUIPERS K, VANHERLE S, POELMANS K, WOLFS E, BOGIE J, VANGANSEWINKEL T.
Lipid alterations in hereditary peripheral neuropathies: common mechanisms in disease heterogeneity?
Molecular Neurodegeneration. 2026 Feb 4. doi: 10.1186/s13024-026-00932-6. (IF=17.5, Q1).

Abstract

While the impact of lipid alterations on central nervous system disorders is well-studied, increasing evidence indicates that lipids also play an important role in the pathology of hereditary peripheral neuropathies (HPN). It is becoming clear that Schwann cells and neurons in peripheral nerves heavily depend on lipids for membrane interactions, (sub)cellular signalling, and the formation of myelin sheaths. In support of this notion, disturbances in the level and composition of lipid classes, including phospholipids, sphingolipids and cholesterol, perturb normal functioning of peripheral nerves. Intriguingly, lipid disturbances seem to be a common denominator within the heterogeneous group of HPN, with hindrances in cholesterol and sphingolipid metabolism primarily influencing Schwann cell and neuron homeostasis, respectively. In this review, we provide an overview of lipid disturbances in various HPN with the goal of finding main commonalities between the different diseases and to identify potential novel treatment strategies.

Keywords: Demyelination; Lipid metabolism; Neurodegeneration; Neurons; Peripheral neuropathy; Schwann cells.

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- LOIX M, VANHERLE S, BOLKAERTS L, VERBERK SGS, PUNT M, WOUTERS F, MOONEN B, VERHAGEN R, VAN WOUW SAE, JONGEJAN A, DISTEL B, ELGERSMA Y, HAIDAR M, ZELCER N, HENDRIKS JJA, BOGIE JFJ.

UBE3A promotes foam cell formation and counters remyelination by targeting ABCA1 for proteasomal degradation.

Nature Communications. 2025 Aug 29;16(1):8077. doi: 10.1038/ s41467-025-62053-w. (IF=15.7, Q1) –

Abstract

The accumulation of foamy macrophages is a pathological hallmark of demyelinating brain disorders. Perturbed metabolism and efflux of intracellular lipids underlie the development of a harmful foamy macrophage phenotype in these disorders, yet, the molecular mechanisms underlying this dysregulation are poorly understood. Here, we show that the ubiquitin-proteasome system controls the turnover of the cholesterol efflux transporter ATP-binding cassette A1 (ABCA1) in lipid-loaded macrophages in the brain. We report that accumulation of myelin-derived lipids promotes the abundance and activity of ubiquitin-protein E3 ligase A (UBE3A) in macrophages, which stimulates ABCA1 ubiquitination and subsequent degradation. This boosts cellular lipid accumulation and induces an inflammatory macrophage phenotype that impairs remyelination. We further establish Tat-interacting protein 30 (TIP30), an inhibitor of importin α -mediated nuclear import, as an essential regulator of cytosolic UBE3A levels. Together, our findings identify UBE3A as a driver of foam cell formation and indicate that targeting UBE3A-mediated ABCA1 degradation is a promising strategy to enhance central nervous system repair.

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- VANHERLE S, LOIX M, MIRON VE, HENDRIKS JJA, BOGIE JFJ.

Lipid metabolism, remodelling and intercellular transfer in the CNS.

Nature Reviews Neuroscience. 2025 Apr;26(4):214-231. doi 10.1038/s41583-025-00908-3. (IF=26.7, Q1)

Abstract

Lipid metabolism encompasses the catabolism and anabolism of lipids, and is fundamental for the maintenance of cellular homeostasis, particularly within the lipid-rich CNS. Increasing evidence further underscores the importance of lipid remodelling and transfer within and between glial cells and neurons as key orchestrators of CNS lipid homeostasis. In this Review, we summarize and discuss the complex landscape of processes involved in lipid metabolism, remodelling and intercellular transfer in the CNS. Highlighted are key pathways, including those

mediating lipid (and lipid droplet) biogenesis and breakdown, lipid oxidation and phospholipid metabolism, as well as cell-cell lipid transfer mediated via lipoproteins, extracellular vesicles and tunnelling nanotubes. We further explore how the dysregulation of these pathways contributes to the onset and progression of neurodegenerative diseases, and examine the homeostatic and pathogenic impacts of environment, diet and lifestyle on CNS lipid metabolism.

Under revision

- JEROEN GUNS, SAM VANHERLE, SAMIKSHA SARDANA, KAI HONG, BRECHT MOONEN, LIEN VAN OTTERDIJK, MELANIE LOIX, KOEN KUIPERS, FLORE WOUTERS, KIRSTEN POELMANS, TESS DIERCKX, LEEN TIMMERMANS, TIM VANGANSEWINKEL, ESTHER WOLFS, BIEKE BROUX, BART GHESQUIÈRE, LUCIANA BEROD, MONIQUE T MULDER, FLORIAN HERMANS, NOAM ZELCER, ERIN M GIBSON, MARC P BAGGELAAR, MIRANDA NABBEN, JEROME JA HENDRIKS, DANTE NECULAI, JOOST JFP LUIKEN, JEROEN FJ BOGIE.

zDHC5-driven FABP5 palmitoylation impairs brain repair by disrupting foam cell physiology.

Nature Reviews Neuroscience (under revision). (IF=21.1, Q1)

Prof. dr. Bieke Broux (UHasselt)

Assistant Professor Immunology

Chronic inflammation and Blood brain barrier disruption in Neurodegeneration (CBN)

Neuroimmune Connections & Repair (NIC&R) lab

Hasselt University – Biomedical Research Institute

Agoralaan, building C – B-3590 Diepenbeek

T +32 11 26 92 54

T +32 468 14 30 54

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ULiège

Dr. Sophie Laguesse (ULiège)

F.R.S-FNRS Research Associate

Giga-Stem Cells, Giga-Neurosciences

Laboratory of molecular regulation of Neurogenesis – Addiction development

Quartier Hôpital

15, Avenue Hippocrate

B-4000 Liège

Belgium

T +32 4 366.59.51

slaguesse@uliege.be

ORCID 0000-0002-9217-0087

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- TIELENS, S.BOUTIN, C.HUYSSSEUNE, S. THELEN N., CHARLET-BRIART, M. REYSKENS, C., OSKERA, L., BOUTSEN, A., MATEO-SANCHEZ, S., DELACROIX, L., LABEDAN, P., THIRY, M., MALGRANGE, B., CHARIOT, A., TISSIR, F., CREPPE, C., SEUNTJENS, E., **LAGUESSE, S.**, AND NGUYEN, L,

Loss of *Elp3* impairs the maturation tempo of brain ependymal cells

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Abstract

Conditional deletion of *Elp3* in the mouse forebrain leads to microcephaly at birth. In this study, we demonstrate that these mice also develop postnatal hydrocephalus, associated with an enlargement of the brain ventricles. In wild-type mice, ependymal motile cilia are properly aligned to facilitate the circulation of cerebrospinal fluid (CSF) within the ventricles. Our findings reveal that *Elp3* loss induces endoplasmic reticulum (ER) stress and upregulation of ATF4 expression in ependymal cell progenitors, which compromises Notch signaling and accelerates their maturation. This is accompanied by a disruption in the establishment of rotational and translational polarities of the motile cilia of maturing ependymal cells, resulting in disorganized cilia bundles. Collectively, these molecular abnormalities lead to the premature and abnormal development of ependymal cells, culminating in cilia beating dysfunction, impaired CSF clearance, and the development of hydrocephalus.

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Queen Elisabeth Medical Foundation – Q.E.M.F.
Königin-Elisabeth-Stiftung für Medizin – K.E.S.M.**

Mailing address:

The scientific director:

Prof. dr. Jean-Marie Maloteaux
3, avenue J.J. Crocq laan
1020 Bruxelles - Brussel
Belgium
Tel.: +32 2 478 35 56
E-mail: jean-marie.maloteaux@uclouvain.be

Secretary:

Mr. Erik Dhondt
3, avenue J.J. Crocq laan
1020 Bruxelles - Brussel
Belgium
Tel.: +32 2 478 35 56
E-mail: fmre.gske@skynet.be
erik.dhondt@skynet.be
e.l.dhondt@skynet.be

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