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2022

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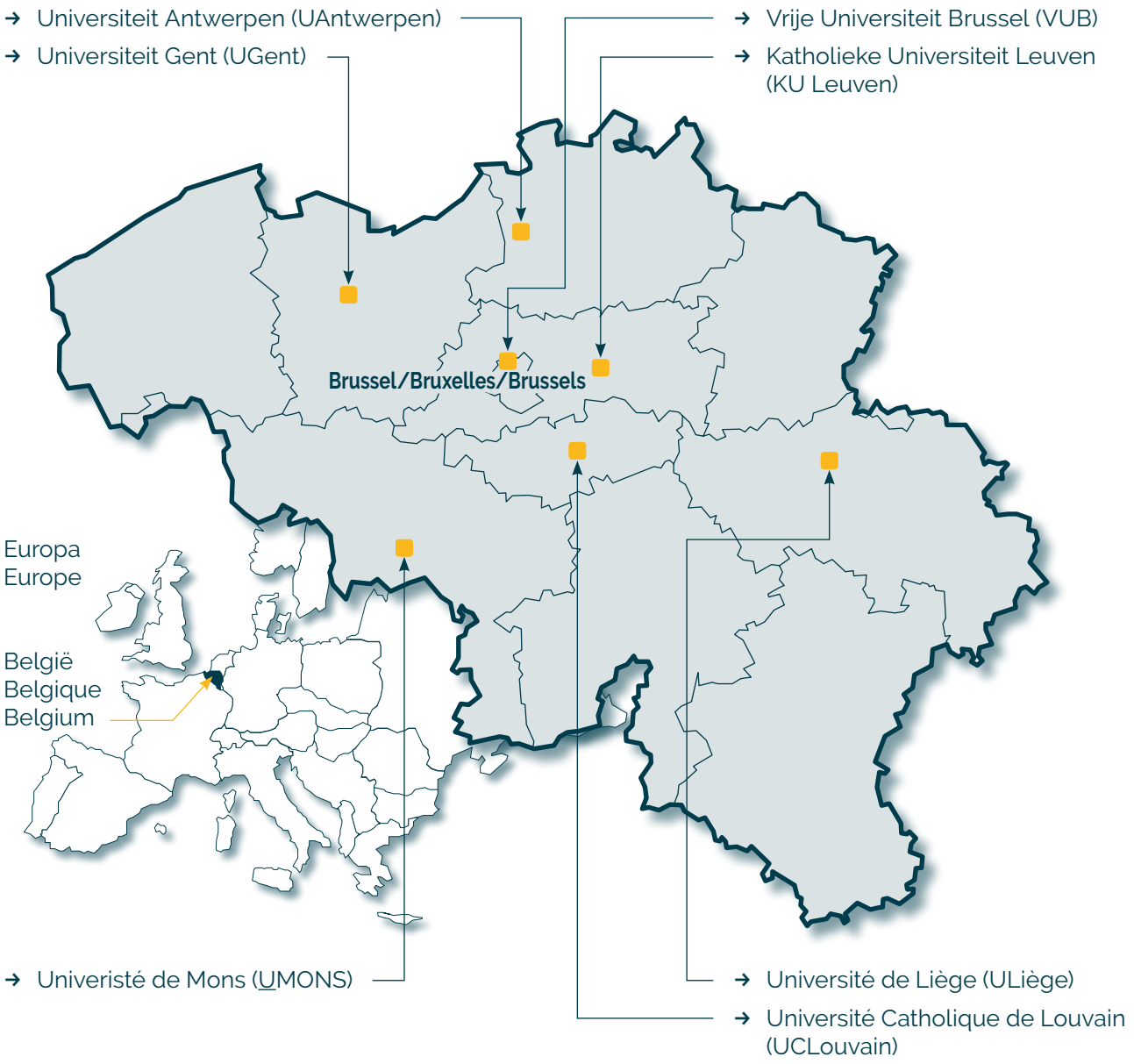

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Publicaties – Publications – Publikationen – Publications

UCLouvain – UMONS – UGent

Prof. dr. Jean-Noël Octave (UCLouvain)
Faculty of Pharmacy and Biomedical Sciences
Institute of neuroscience (IONS)
CEMO
Avenue Hippocrate 54/B1.54.10
1200 Woluwe-Saint-Lambert
jean-noel.octave@uclouvain.be

Prof. dr. Philippe Gailly (UCLouvain)
Institute of Neuroscience (IoNS)
Laboratory of Cell Physiology (FYCL)
Avenue Mounier, 53 - B1.53.17
1200 Brussels
philippe.gailly@uclouvain.be
Tel. + 32 (0)2 764 55 42

Prof. dr. Nathalie Pierrot (UCLouvain)
Institute of Neuroscience (IONS)
CEMO
Avenue Mounier 53/B1.53.03
1200 Woluwe-Saint-Lambert
nathalie.pierrot@uclouvain.be

Prof dr. Laurence Ris (UMONS)
Lecturer, head of the department of Neuroscience
Faculty of Medicine and Pharmacy
6A, avenue du Champ de Mars 7000 Mons
laurence.ris@umons.ac.be

Prof. dr. Paul Boon (UGent)
Professor and chairman Department of Neurology
Chairman Division of Head, Movement and Senses
Ghent University Hospital - Ghent University
10 Corneel Heymanslaan
9000 Gent
Paul.boon@ugent.be

Robrecht Raedt (UGent)

Publications in 2022/2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- Kreis A, Yerna X, Schakman O, Issa F, de Clippele M, Tajeddine N, Pierrot N, Octave JN, Gualdani R, Gailly P. (2023)
  Conditional deletion of KCC2 impairs synaptic plasticity and both spatial and nonspatial memory.
  Frontiers in Molecular Neuroscience, IF:5,64; Q1; 2023 Apr 24;16:1081657doi: 10.3389/fnmol.2023.1081657.

Abstract

The postsynaptic inhibition through $GABA_A$ receptors ($GABA_AR$) relies on two mechanisms, a shunting effect due to an increase in the postsynaptic membrane conductance and, in mature neurons, a hyperpolarization effect due to an entry of chloride into postsynaptic neurons. The second effect requires the action of the K^+-Cl^- cotransporter KCC2 which extrudes Cl^- from the cell and maintains its cytosolic concentration very low. Neuronal chloride equilibrium seems to be dysregulated in several neurological and psychiatric conditions such as epilepsy, anxiety, schizophrenia, Down syndrome, or Alzheimer›s disease. In the present study, we used the KCC2 Cre-lox knockdown system to investigate the role of KCC2 in synaptic plasticity and memory formation in adult mice. Tamoxifen-induced conditional deletion of KCC2 in glutamatergic neurons of the forebrain was performed at 3 months of age and resulted in spatial and nonspatial learning impairment. On brain slices, the stimulation of Schaffer collaterals by a theta burst induced long-term potentiation (LTP). The lack of KCC2 did not affect potentiation of field excitatory postsynaptic potentials (fEPSP) measured in the stratum radiatum (dendrites) but increased population spike (PS) amplitudes measured in the CA1 somatic layer, suggesting a reinforcement of the EPSP-PS potentiation, i.e., an increased ability of EPSPs to generate action potentials. At the cellular level, KCC2 deletion induced a positive shift in the reversal potential of $GABA_AR$-driven Cl^- currents (E_{GABA}), suggesting an intracellular accumulation of chloride subsequent to the downregulation of KCC2. After treatment with bumetanide, an antagonist of the Na^+-K^+-Cl^- cotransporter NKCC1, spatial memory impairment, chloride accumulation, and EPSP-PS potentiation were rescued in mice lacking KCC2. The presented results emphasize the importance of chloride equilibrium and GABA-inhibiting ability in synaptic plasticity and memory formation.

Keywords: GABA signaling; chloride transporters; hippocampus; long term potentiation; memory.

Funding

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Geneeskundige Stichting Koningin Elisabeth
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Publicaties – Publications – Publikationen – Publications

UCLouvain – ULiege – UGent

UCLouvain :
Prof. dr. Pascal Kienlen-Campard (PI, spokesperson) – partner 1 (P1)
Institute of Neuroscience
IONS-CEMO, Avenue Mounier 53 bte B1.53.02
B-1200 Brussels

Prof. Bernard Hanseeuw, PhD and **Adrian Ivanoiu** (collaborators) – partner 2 (P2)
Cliniques St Luc, UCLouvain
IoNS- NEUR

ULiège
Prof. dr. Loïc Quinton (PI) – partner 3 (P3)
MS-LAB, UR MolSys
Allée du six Aout 11 - Quartier Agora - Liège Université
B4000 -Liège 1

Ghent University
Prof. dr. Jan Gettemans – partner 4 (P4)
Department of Biomolecular Medicine
Faculty of Medicine & Health Sciences
Campus Ardoyen
Technology Lane 75
B-9052 Ghent

Publication 2022/2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- Papadopoulos, N., Suelves, N., Perrin, F., Vadukul, D.M., Vrancx, C., Constantinescu, S.N., and Kienlen-Campard, P. (2022).
Structural Determinant of beta-Amyloid Formation: From Transmembrane Protein Dimerization to beta- Amyloid Aggregates.
Biomedicines 10. 10.3390/biomedicines10112753 (IF 4.76).Q1

Abstract:
Most neurodegenerative diseases have the characteristics of protein folding disorders, i.e., they cause lesions to appear in vulnerable regions of the nervous system, corresponding to protein aggregates that progressively spread through the neuronal network as the symptoms progress. Alzheimer's disease is one of these diseases. It is characterized by two types of lesions: neurofibrillary tangles (NFTs) composed of tau proteins and senile plaques, formed essentially of amyloid peptides (A). A combination of factors ranging from genetic mutations to age-related changes in the cellular context converge in this disease to accelerate A deposition. Over the last two decades, numerous studies have attempted to elucidate how structural determinants of its precursor (*APP*) modify A production, and to understand the processes leading to the formation of different A aggregates, e.g., fibrils and oligomers. The synthesis proposed in this review indicates that the same motifs can control *APP* function and A production essentially by regulating membrane protein dimerization, and subsequently A aggregation processes. The distinct properties of these motifs and the cellular context regulate the *APP* conformation to trigger the transition to the amyloid pathology. This concept is critical to better decipher the patterns switching *APP* protein conformation from physiological to pathological and improve our understanding of the mechanisms underpinning the formation of amyloid fibrils that devastate neuronal functions.
Keywords: APP-C99; Alzheimer's disease; Amyloid Precursor Protein; aggregation; amyloid beta; dimerization; oligomerization; orientations.

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- Decoene, K.W., K. Unal, A. Staes, O. Zwaenepoel, J. Gettemans, K. Gevaert, J.M. Winne, and A. Madder. 2022.
Triazolinedione protein modification: from an overlooked off-target effect to a tryptophan-based bioconjugation strategy.
Chem Sci. 13:5390-5397 (IF=9,825). Q1- PMID: **35655564** - PMCID: PMC9093138 - DOI: 10.1039/d1sc06942j

Abstract:
Labelling of tyrosine residues in peptides and proteins has been reported to selectively occur *via* a 'tyrosine-click' reaction with triazolinedione reagents (TAD). However, we here demonstrate that TAD reagents are actually not selective for tyrosine and that tryptophan

residues are in fact also labelled with these reagents. This off-target labelling remained under the radar as it is challenging to detect these physiologically stable but thermally labile modifications with the commonly used HCD and CID MS/MS techniques. We show that selectivity of tryptophan over tyrosine can be achieved by lowering the pH of the aqueous buffer to effect selective Trp-labelling. Given the low relative abundance of tryptophan compared to tyrosine in natural proteins, this results in a new site-selective bioconjugation method that does not rely on enzymes nor unnatural amino acids and is demonstrated for peptides and recombinant proteins.

- Grobler, C., M. van Tongeren, J. Gettemans, D.B. Kell, and E. Pretorius. 2023.
Alzheimer's Disease: A Systems View Provides a Unifying Explanation of Its Development.
J Alzheimers Dis. 91:43-70 (IF=4,472). Q2; PMID: **36442193** - DOI: 10.3233/JAD-220720

Abstract
Alzheimer's disease (AD) is a debilitating neurodegenerative disorder affecting 50 million people globally. It is characterized by the presence of extracellular senile plaques and intracellular neurofibrillary tangles, consisting of amyloid- and hyperphosphorylated tau proteins, respectively. Despite global research efforts, there is currently no cure available, due in part to an incomplete understanding of the disease pathogenesis. Numerous possible mechanisms, or hypotheses, explaining the origins of sporadic or late-onset AD have been proposed, including the amyloid-, inflammatory, vascular, and infectious hypotheses. However, despite ample evidence, the failure of multiple trial drugs at the clinical stage illuminates the possible pitfalls of these hypotheses. Systems biology is a strategy which aims to elucidate the interactions between parts of a whole. Using this approach, the current paper shows how the four previously mentioned hypotheses of AD pathogenesis can be intricately connected. This approach allows for seemingly contradictory evidence to be unified in a system-focused explanation of sporadic AD development. Within this view, it is seen that infectious agents, such as P. gingivalis, may play a central role. The data presented here shows that when present, P. gingivalis or its virulence factors, such as gingipains, may induce or exacerbate pathologies underlying sporadic AD. This evidence supports the view that infectious agents, and specifically P. gingivalis, may be suitable treatment targets in AD.
Keywords: Alzheimer's disease; infectious agents; systemic inflammation; systems biology.

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- Malotaux V, Dricot L, Quenon L, Lhommel R, Ivanoiu A, Hanseeuw B. (2022)
Default-Mode Network Connectivity Changes During the Progression Toward Alzheimer's Dementia: A Longitudinal Functional Magnetic Resonance Imaging Study.
Brain Connectivity. IF = 2.26; Q4; 2023 Jun, 13 (5): 287-296. Doi 10.1089/brain.2022.0008.
Epub 2022, oct 10

Abstract
Background/Purpose: Brain function changes with Alzheimer›s disease (AD) progression. Evaluating those changes longitudinally is important to understand the complex relationships between brain pathologies and cognition. We aimed (1) to identify longitudinal changes in

functional connectivity in patients with mild cognitive impairment (MCI) characterized for amyloid- (A) status and (2) to relate these functional changes to clinical progression.
Methods: Forty-four patients with MCI were followed using serial functional magnetic resonance imaging (fMRI) over 1.2 years (three sessions) and cognitive testing over 3.1 years (five sessions). Intra and inter-network connectivities were computed to assess changes in brain connectivity using a network atlas adapted for late adulthood. Sixteen low-A clinically normal older adults underwent a single fMRI session for group comparisons at baseline. Linear mixed-effects models with random intercept and slope were used to predict changes in connectivity based on A status and progression to dementia.
Results: At baseline, intra and inter-network resting-state fMRI connectivities did not differ by baseline clinical diagnosis, A status, or clinical progression to dementia. At the final imaging session, progressive MCI had significantly higher connectivity compared with stable MCI, specifically within the default-mode network (DMN). Longitudinally, progressive MCI had increasing intra-DMN connectivity over time compared with stable MCI, and the rate of changes in connectivity was significantly associated with the rate of cognitive decline.
Conclusions: Intra-DMN connectivity increases in MCI patients progressing toward dementia, suggesting aberrant synchronization in the symptomatic stages of AD. Impact statement Changes in functional connectivity occur in the course of Alzheimer's disease. We observed a progressive increase over time in resting-state functional connectivity within the default-mode network in patients with mild cognitive impairment who progressed to dementia. The rate of connectivity increase was significantly associated with the rate of cognitive decline. The observation of increased functional connectivity during the progression to dementia, and not only in the pre-clinical stage, is interpreted as an aberrant synchronization rather than a compensation mechanism.
Keywords: aging; amyloid; default-mode network; dementia; mild cognitive impairment; resting-state fMRI.

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- Lebrun L; Hanseeuw B; Van Pesch V ; Ivanoiu A. (2022)
Alzheimer disease's cerebrospinal fluid biomarkers differences between immigrants and natives in a Belgian memory clinic.
Acta Neurologica Belgica. IF = 2.4, Q4, 2023 apr 123(2): 537-544 doi: 10.1007/s13760-022-02143-4. Epub 2022 Nov 14.

Abstract
Background: Diagnosis of neurodegenerative diseases can raise difficulties among immigrant patients due to language, educational or sociocultural differences with natives. CSF biomarkers of Alzheimer's disease are useful tools to early diagnose neurodegeneration. Yet very few studies have investigated differences of those biomarkers between immigrant and native populations.
Objective: We aimed to characterize differences between CSF biomarkers of Alzheimer's disease within Belgian native and immigrant patients analyzed at Saint Luc Neurochemistry Lab (Brussels, Belgium).
Methods: CSF samples from patients consulting at Saint Luc Memory Clinic (n = 356) or at others hospitals (n = 2430) were analyzed by Saint Luc Neurochemistry Lab between 2010 and 2014. We conducted linear regressions predicting CSF biomarkers with demographic data:

age, sex and presumed ethnic origin. For the last one, we subdivided the cohort in natives and immigrants according to their surnames.
Results: Immigrant patients benefit from a CSF sample analysis at a younger age than natives ($p < 0.001$). After linear regressions, age showed a significant impact on all biomarkers ($p < 0.005$). Ethnicity showed a significant impact on T-Tau ($p = 0.007$) and on T-Tau/amyloid-42 ratio ($p = 0.009$). Sex showed a significant impact on T-Tau ($p = 0.002$). ANCOVA analysis suggested that the effect of Age on A_{42} manifests differently according to the ethnicity of the individual.
Conclusion: This study shows higher T-Tau and T-Tau/amyloid-42 ratio values in younger native patients from a Belgian Memory Clinic. A_{42} values tend to follow a different dynamic in time according to the ethnic origin of patients, with pathological values at older ages in immigrants.
Keywords: Alzheimer's disease; Biomarkers; Cerebrospinal fluid; Ethnicity.

Acknowledgments
B. Hanseeuw is supported by the Fonds National de la Recherche Scientifique (SPD #40000041), the Alzheimer Research Foundation (SAO-FRA), and the Fondation Médicale Reine Elisabeth (F.M.R.E.).

- Gettemans J.
Site-Specific Fluorescent Labeling, Single-Step Immunocytochemistry and Delivery of Nanobodies into Living Cells.
Method in Molecular Biology vol 2246. (IF: 38.31; **Q3**). 2022. PMID: 35157284

Abstract
The smallest natural antibody fragments currently available are single-domain antibodies obtained from camelid species and sharks (variable new antigen receptors). These molecules consist of a single amino acid chain of ~120 amino acids that adopts a typical immunoglobulin fold. Single-domain antibodies (nanobodies) are monovalent and can be isolated from immunized animals, from naïve libraries, or from synthetic libraries. Importantly, their complete DNA sequences are readily obtained by default, which greatly facilitates their rapid manipulation for various applications. Here, a PCR-based protocol for inserting a sortase A recognition sequence at the carboxy-terminus of a nanobody is described. Subsequently, a sortase A-catalyzed biochemical reaction results in tagging of the nanobody with a short carboxy-terminal amino acid sequence that carries a non-canonical residue (propargyl glycine). This allows click chemistry to be performed with an azido-derivatized fluorophore, with the ensuing fluorescent nanobody being covalently and site-specifically labeled. The labeled nanobody can be used directly for immunocytochemistry, omitting the classical secondary antibody step. Also described are methods for delivery of fluorescent nanobodies into the cytoplasm of mammalian cells by photoporation, a very low-toxicity approach involving laser light and graphene quantum dots. The combined protocol embodies a novel route for studying protein function in living cells at high resolution.
Keywords: Fluorescence; Immunocytochemistry; Intrabody; Nanobody; Single-domain antibody; Single-step staining; Site-directed labeling; Sortase; VHH.

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Geneeskundige Stichting Koningin Elisabeth
Fondation Médicale Reine Elisabeth
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Publicaties – Publications – Publikationen – Publications

VUB – UGent

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

Publication 2022/2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- Deborah C.W. Klooster, Michael A. Ferguson, Paul A.J.M. Boon, and Chris Baeken
Personalizing Repetitive Transcranial Magnetic Stimulation Parameters for Depression Treatment Using Multimodal Neuroimaging
Biol Psychiatry Cogn Neurosci Neuroimaging (IF: 6.2; **Q1**) 2022 Jun;7(6):536-545.
Doi: 10.1016/j.bpsc.2021.11.004. Epub 2021 Nov 17.

Abstract
Repetitive transcranial magnetic stimulation (rTMS) is a tool that can be used to administer treatment for neuro- psychiatric disorders such as major depressive disorder, although the clinical efficacy is still rather modest. Overly general stimulation protocols that consider neither patient-specific depression symptomology nor individualized brain characteristics, such as anatomy or structural and functional connections, may be the cause of the high inter- and intraindividual variability in rTMS clinical responses. Multimodal neuroimaging can provide the necessary insights into individual brain characteristics and can therefore be used to personalize rTMS parameters. Optimal coil positioning should include a three-step process: 1) identify the optimal (indirect) target area based on the exact symptom pattern of the patient; 2) derive the cortical (direct) target location based on functional and/or structural connectomes derived from functional and diffusion magnetic resonance imaging data; and 3) determine the ideal coil position by computational modeling, such that the electric field distribution overlaps with the cortical target. These TMS-induced electric field simulations, derived from anatomical and diffusion magnetic resonance imaging data, can be further applied to compute optimal stimulation intensities. In addition to magnetic resonance imaging, electroencephalography can provide complementary information regarding the ongoing brain oscillations. This information can be used to determine the optimal timing and frequency of the stimuli. The heightened benefits of these personalized stimu- lation approaches are logically reasoned, but speculative. Randomized clinical trials will be required to compare clinical responses from standard rTMS protocols to personalized protocols. Ultimately, an optimized clinical response may result from precision protocols derived from combinations of personalized stimulation parameters.
Keywords: Depression; Electroencephalography; Magnetic resonance imaging; Personalized medicine; Transcranial magnetic stimulation.

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- Wietse A. Wiels, Mandy M. J. Wittens, Dieter Zeeuws, C hris Baeken and Sebastiaan Engelborghs
Neuropsychiatric Symptoms in Mild Cognitive Impairment and Dementia Due to AD: Relation With Disease Stage and Cognitive Deficits
Front Psychiatry (IF: 4.16; Q2). 2021. PMID: 34483998

Abstract

Background: The interaction between neuropsychiatric symptoms, mild cognitive impairment (MCI), and dementia is complex and remains to be elucidated. An additive or multiplicative effect of neuropsychiatric symptoms such as apathy or depression on cognitive decline has been suggested. Unraveling these interactions may allow the development of better prevention and treatment strategies. In the absence of available treatments for neurodegeneration, a timely and adequate identification of neuropsychiatric symptom changes in cognitive decline is highly relevant and can help identify treatment targets.

Methods: An existing memory clinic-based research database of 476 individuals with MCI and 978 individuals with dementia due to Alzheimer's disease (AD) was reanalyzed. Neuropsychiatric symptoms were assessed in a prospective fashion using a battery of neuropsychiatric assessment scales: Middelheim Frontality Score, Behavioral Pathology in Alzheimer's Disease Rating Scale (Behave-AD), Cohen-Mansfield Agitation Inventory, Cornell Scale for Depression in Dementia (CSDD), and Geriatric Depression Scale (30 items). We subtyped subjects suffering from dementia as mild, moderate, or severe according to their Mini-Mental State Examination (MMSE) score and compared neuropsychiatric scores across these groups. A group of 126 subjects suffering from AD with a significant cerebrovascular component was examined separately as well. We compared the prevalence, nature, and severity of neuropsychiatric symptoms between subgroups of patients with MCI and dementia due to AD in a cross-sectional analysis.

Results: Affective and sleep-related symptoms are common in MCI and remain constant in prevalence and severity across dementia groups. Depressive symptoms as assessed by the CSDD further increase in severe dementia. Most other neuropsychiatric symptoms (such as agitation and activity disturbances) progress in parallel with severity of cognitive decline. There are no significant differences in neuropsychiatric symptoms when comparing "pure" AD to AD with a significant vascular component.

Conclusion: Neuropsychiatric symptoms such as frontal lobe symptoms, psychosis, agitation, aggression, and activity disturbances increase as dementia progresses. Affective symptoms such as anxiety and depressive symptoms, however, are more frequent in MCI than mild dementia but otherwise remain stable throughout the cognitive spectrum, except for an increase in CSDD score in severe dementia. There is no difference in neuropsychiatric symptoms when comparing mixed dementia (defined here as AD + significant cerebrovascular disease) to pure AD.

Keywords: behavioral and psychological symptoms of dementia, neuropsychiatric symptoms, mild cognitive impairment, Alzheimer's disease, depressive symptoms, memory clinic

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- Hamed Ekhtiari, Peyman Ghobadi-Azbari, Axel Thielscher, Andrea Antal, Lucia M. Li, A. Duke Shereen, Yuranny Cabral-Calderin, Daniel Keeser, Til Ole Bergmann, Asif Jamil, Ines R. Violante, Jorge Almeida, Marcus Meinzer, Hartwig R. Siebner Adam J. Woods, Charlotte J. Stagg, Rany Abend, Daria Antonenko, Tibor Auer , Marc Bächinger, Chris Baeken, Helen C. Barron, Henry W. Chase, Jenny Crinion, Abhishek Datta, Matthew H. Davis, Mohsen Ebrahimi, Zeinab Esmaeilpour, Brian Falcone, Valentina Fiori, Iman Ghodratitoostani , Gadi Gilam, Roland H. Grabner, Joel D. Greenspan, Georg Groen, Gesa Hartwigsen, Tobias U. Hauser, Christoph S. Herrmann, Chi-Hung Juan, Bart Krekelberg, Stephanie Lefebvre, Sook-Lei Liew, Kristoffer H. Madsen, Rasoul Mahdavifar-Khayati, Nastaran Malmir, Paola Marangolo, Andrew K. Martin, Timothy J. Meeker, Hossein Mohaddes Ardabili, Marius Moisa, Davide Momi, Beni Mulyana,

Alexander Opitz, Natasza Orlov, Patrick Ragert, Christian C. Ruff, Giulio Ruffini, Michaela Ruttorf, Arshiya Sangchooli , Klaus Schellhorn, Gottfried Schlaug, Bernhard Sehm, Ghazaleh Soleimani, Hosna Tavakoli, Benjamin Thompson, Dagmar Timmann, Aki Tsuchiyagaito, Martin Ulrich, Johannes Vosskuhl, Christiane A. Weinrich, Mehran Zare-Bidoky, Xiaochu Zhang, Benedikt Zoefel, Michael A. Nitsche and Marom Bikson

A checklist for assessing the methodological quality of concurrent tES-fMRI studies (ContES checklist): a consensus study and statement

Nat Protoc (IF: 13.49; **Q1**), 2022 Mar;17(3):596-617. doi: 10.1038/s41596-021-00664-5. Epub 2022 Feb 4.

Abstract

Low-intensity transcranial electrical stimulation (tES), including alternating or direct current stimulation, applies weak electrical stimulation to modulate the activity of brain circuits. Integration of tES with concurrent functional MRI (fMRI) allows for the mapping of neural activity during neuromodulation, supporting causal studies of both brain function and tES effects. Methodological aspects of tES-fMRI studies underpin the results, and reporting them in appropriate detail is required for reproducibility and interpretability. Despite the growing number of published reports, there are no consensus-based checklists for disclosing methodological details of concurrent tES-fMRI studies. The objective of this work was to develop a consensus-based checklist of reporting standards for concurrent tES-fMRI studies to support methodological rigor, transparency and reproducibility (ContES checklist). A two-phase Delphi consensus process was conducted by a steering committee (SC) of 13 members and 49 expert panelists through the International Network of the tES-fMRI Consortium. The process began with a circulation of a preliminary checklist of essential items and additional recommendations, developed by the SC on the basis of a systematic review of 57 concurrent tES-fMRI studies. Contributors were then invited to suggest revisions or additions to the initial checklist. After the revision phase, contributors rated the importance of the 17 essential items and 42 additional recommendations in the final checklist. The state of methodological transparency within the 57 reviewed concurrent tES-fMRI studies was then assessed by using the checklist. Experts refined the checklist through the revision and rating phases, leading to a checklist with three categories of essential items and additional recommendations: (i) technological factors, (ii) safety and noise tests and (iii) methodological factors. The level of reporting of checklist items varied among the 57 concurrent tES-fMRI papers, ranging from 24% to 76%. On average, 53% of checklist items were reported in a given article. In conclusion, use of the ContES checklist is expected to enhance the methodological reporting quality of future concurrent tES-fMRI studies and increase methodological transparency and reproducibility.

Acknowledgments

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- Tasha Poppa, Lars Benschop, Paula Horczak, Marie-Anne Vanderhasselt , Evelien Carrette , Antoine Bechara , Chris Baeken, Kristl Vonck
Auricular transcutaneous vagus nerve stimulation modulates the heart-evoked potential
Brain Stimul (IF: 8.96; **Q1**), 2022 Jan-Feb;15(1):260-269, doi: 10.1016/j.brs.2021.12.004. Epub 2021 Dec 18.

Abstract
Background: There is active interest in biomarker discovery for transcutaneous auricular vagus nerve stimulation (taVNS). However, greater understanding of the neurobiological mechanisms is needed to identify candidate markers. Accumulating evidence suggests that taVNS influences activity in solitary and parabrachial nuclei, the primary brainstem relays for the transmission of visceral sensory afferents to the insula. The insula mediates interoception, which concerns the representation and regulation of homeostatic bodily states. Consequently, interoceptive pathways may be relevant to taVNS mechanisms of action.
Hypotheses: We hypothesized that taVNS would modulate an EEG-derived marker of interoceptive processing known as the heart-evoked potential (HEP). We also hypothesized that taVNS-induced HEP effects would be localizable to the insula.
Methods: Using a within-subject, sham-controlled design, we recorded EEG and ECG concurrent to taVNS in 43 healthy adults. Using ECG and EEG data, we extracted HEPs. Estimation of the cortical sources of the taVNS-dependent HEP responses observed at the scalp were computed using the Boundary Element Method and weighted Minimum Norm Estimation. Statistics were calculated using cluster-based permutation methods.
Results: taVNS altered HEP amplitudes at frontocentral and centroparietal electrode sites at various la- tencies. The taVNS-dependent HEP effect was localized to the insula, operculum, somatosensory cortex, and orbital and ventromedial prefrontal regions.
Conclusion: The results support the hypothesis that taVNS can access the insula as well as functionally and anatomically connected brain regions. HEPs may serve as an objective, non-invasive outcome parameter for the cortical effects of taVNS.

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- Luqing Wei', Chris Baeken, Daihong Liu, Jiuquan Zhan and Guo-Rong Wu
Functional connectivity–based prediction of global cognition and motor function in riluzole-naive amyotrophic lateral sclerosis patients
Netw Neurosci (IF: 4.62; **Q2**) 2022 Feb 1;6(1):161-174. doi: 10.1162/netn_a_00217. eCollection 2022 Feb.

Abstract
Amyotrophic lateral sclerosis (ALS) is increasingly recognized as a multisystem disorder accompanied by cognitive changes. To date, no effective therapy is available for ALS patients, partly due to disease heterogeneity and an imperfect understanding of the underlying pathophysiological processes. Reliable models that can predict cognitive and motor deficits are needed to improve symptomatic treatment and slow down disease progression. This study

aimed to identify individualized functional connectivity–based predictors of cognitive and motor function in ALS by using multiple kernel learning (MKL) regression. Resting-state fMRI scanning was performed on 34 riluzole-naive ALS patients. Motor severity and global cognition were separately measured with the revised ALS functional rating scale (ALSFRS-R) and the Montreal Cognitive Assessment (MoCA). Our results showed that functional connectivity within the default mode network (DMN) as well as between the DMN and the sensorimotor network (SMN), fronto-parietal network (FPN), and salience network (SN) were predictive for MoCA scores. Additionally, the observed connectivity patterns were also predictive for the individual ALSFRS-R scores. Our findings demonstrate that cognitive and motor impairments may share common connectivity fingerprints in ALS patients. Furthermore, the identified brain connectivity signatures may serve as novel targets for effective disease-modifying therapies.
Keywords: Amyotrophic lateral sclerosis; Cognitive changes; Functional connectivity; Motor severity.

Funding
This work was also supported by the Queen Elisabeth Medical Foundation for Neurosciences, by the Ghent University Multidisciplinary Research Partnership "The Integrative Neu- roscience of Behavioral Control," a grant BOF16/GOA/017 for a Concerted Research Action of Ghent University, 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) and FWO project G011018N.

- Luqing Wei, Tingting Weng, Hui Dong, Chris Baeken, Ting Jiang [b] and Guo-Rong Wu
The Cortico-basal-cerebellar Neurocircuit is Linked to Personality Trait of Novelty Seeking
Neuroscience (IF: 3.59; **Q3**), 2022 Apr 15;488:96-101. doi: 10.1016/j.
neuroscience.2022.02.027. Epub 2022 Feb 25.

Abstract
Previous neuroimaging studies have highlighted the role of the prefrontal-subcortical circuits in per- sonality trait of novelty seeking (NS), thought to be mediated by the dopaminergic system. However, it remains largely unknown whether cortico-basal-cerebellar connections, heavily influenced by dopamine, are implicated in this temperament dimension as well. The present study aimed to further investigate the relationship between the NS trait and the cortico-basal-cerebellar pathways by using structural covariance network analysis. Ninety- five healthy female volunteers were included in this work, and NS was assessed with the Temperament and Char- acter Inventory (TCI). Our results showed that NS scores were associated with structural connections between the cerebellum and the cerebral cortex, thalamus, and basal ganglia, substantiating the implication of the cortico- basal-cerebellar circuits in the NS construct. In addition, structural connections between visual and sensorimotor regions were also associated with NS scores, indicating that sensory and motor information processing may con- tribute to NS-related behaviors. Overall, the current findings may deepen our understanding of brain structural circuits related to this temperament dimension. ! 2022 IBRO. Published by Elsevier Ltd. All rights reserved.
Keywords: novelty seeking, cortico-basal-cerebellar connections, structural covariance network, temperament and character in- ventory.

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through Science and Technology (IWT), part of the Research Foundation - Flanders (FWO) PrevenD Project 2.0 (T000720N).

- Guo-Rong Wu and Chris Baeken
Individual interregional perfusion between the left dorsolateral prefrontal cortex stimulation targets and the subgenual anterior cortex predicts response and remission to aiTBS treatment in medication-resistant depression: The influence of behavioral inhibition
Brain Stimul (IF: 8.96; **Q1**) 2022 Jan-Feb;15(1):182-189. doi: 10.1016/j.brs.2021.12.003. Epub 2021 Dec 10.

Abstract
Background: Accelerated intermittent Theta Burst Stimulation (aiTBS) has been put forward as an effective treatment to alleviate depressive symptoms. Baseline functional connectivity (FC) patterns between the left dorsolateral prefrontal cortex (DLPFC) and the subgenual anterior cortex (sgACC) have gained a lot of attention as a potential biomarker for response. However, arterial spin labeling (ASL) - measuring regional cerebral blood flow - may allow a more straightforward physiological interpretation of such interregional functional connections.
Objectives: We investigated whether baseline covariance perfusion connectivity between the individu- ally stimulated left DLPFC targets and sgACC could predict meaningful clinical outcome. Considering that individual characteristics may influence efficacy prediction, all patients were also assessed with the Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) scale.
Methods: After baseline ASL scanning, forty-one medication-resistant depressed patients received twenty sessions of neuronavigated left DLPFC aiTBS in an accelerated sham-controlled crossover fashion, where all stimulation sessions were spread over four days (Trial registration: http://clinicaltrials.gov/ show/NCT01832805).
Results: Stronger individual baseline interregional covariance perfusion connectivity patterns predicted response and/or remission. Furthermore, responders and remitters with higher BIS scores displayed stronger baseline interregional perfusion connections.
Conclusions: Targeting the left DLPFC with aiTBS based on personal structural imaging data only may not be the most optimal method to enhance meaningful antidepressant responses. Individual baseline interregional perfusion connectivity could be an important added brain imaging method for individual optimization of more valid stimulation targets within the left DLPFC. Additional therapies dealing with behavioral inhibition may be warranted.
Keywords: Accelerated iTBS; Arterial spin labeling; BIS/BAS; Major depressive disorder; Personalization.

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- Guo-Rong Wu and Chris Baeken
Lateralized subgenual ACC metabolic connectivity patterns in refractory melancholic depression: does it matter?
Cereb Cortex (IF: 5.36; **Q1**), 2023 Mar 21;33(7):3490-3497, doi: 10.1093/cercor/bhac286.

Abstract
Although treatment resistance to antidepressant pharmacotherapy is quite common, the phenomenon of refractory major depressive disorder (rMDD) is not well understood. Nevertheless, the metabolic activity of the subgenual anterior cingulate cortex (sgACC) has been put forward as a possible metabolic biomarker of clinical prediction and response, albeit sgACC lateralization differences in functional connectivity have not yet been extensively examined. Also not in the refractory depressed state. To examine sgACC lateralization differences in metabolic connectivity, we recruited 43 right-handed antidepressant-free unipolar melancholic rMDD patients and 32 right-handed healthy controls to participate in this ^{18}FDG PET study and developed a searchlight-based interregional covariance connectivity approach. Compared to non-depressed individuals, sgACC covariance analysis showed stronger metabolic connections with frontolimbic brain regions known to be affected in the depressed state. Furthermore, whereas the left sgACC showed stronger metabolic connections with ventromedial prefrontal cortical regions, implicated in anhedonia, suicidal ideation, and self- referential processes, the right sgACC showed significantly stronger metabolic connections with posterior hippocampal and cerebellar regions, respectively specialized in memory and social processing. Overall, our results substantiate earlier research that the sgACC is a metabolic key player when clinically depressed and that distinct lateralized sgACC metabolic connectivity patterns are presen

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- Guanzhong Yao · Luqing Wei · Ting Jiang · Hui Dong · Chris Baeken · Guo-Rong Wu
Neural mechanisms underlying empathy during alcohol abstinence: evidence from connectome-based predictive modeling
Brain Imaging Behav (IF: 3.98; **Q2**), 2022 Dec;16(6):2477-2486, doi: 10.1007/s11682-022-00702-0. Epub 2022 Jul 13.

Abstract
Empathy impairments have been linked to alcohol dependence even during abstinent periods. Nonetheless, the neural underpinnings of abstinence-induced empathy deficits remain unclear. In this study, we employed connectome-based pre- dictive modeling (CPM) by using whole brain resting-state functional connectivity (rs-FC) to predict empathy capability of abstinent alcoholics (n=47) versus healthy controls (n=59). In addition, the generalizability of the predictive model (i.e., one group treated as a training dataset and another one treated as a test dataset) was performed to determine whether healthy controls and abstinent alcoholics share common neural fingerprints of empathy. Our results showed that abstinent alcoholics relative to healthy controls had decreased empathy capacity. Although no predictive models were observed in the abstinence group, we found that individual empathy scores in the healthy group can be reliably predicted by functional connectivity from the default mode network (DMN) to the sensorimotor

network (SMN), occipital network, and cingulo- opercular network (CON). Moreover, the identified connectivity fingerprints of healthy controls could be generalized to predict empathy in the abstinence group. These findings indicate that neural circuits accounting for empathy may be disrupted by alcohol use and the impaired degree varies greatly among abstinent individuals. The large inter-individual variation may impede identification of the predictive model of empathy in alcohol abstainers.
Keywords: Abstinent alcoholics · Empathy · Connectome-based predictive modeling

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- Sam L.B. Bonduelle, Rudi De Raedt, Caroline Braet, Edward Campforts , Chris Baeken
Parental criticism affects adolescents' mood and ruminative state: Self-perception appears to influence their mood response
J Exp Child Psychol (IF: 2.61; **Q2)**, 2023 Nov;235:105728, doi: 10.1016/j.jecp.2023.105728. Epub 2023 Jun 28.

Abstract
Feeling and/or being criticized is a known risk factor for various psychiatric disorders in adolescents. However, the link between the experience of social stressors and the development of psy- chopathological symptoms is not yet fully understood. Identifying which adolescent subgroups are more vulnerable to parental criticism could be of great clinical relevance. In this study, 90 nondepressed 14- to 17-year-old adolescents were exposed to a sequence of auditory segments with a positive, neutral, and finally negative valence, mirroring parental criticism. Their mood and ruminative states were assessed before and after exposure to crit- icism. We observed an overall increase in mood disturbance and ruminative thoughts. Self- perception appeared to influence these mood changes, whereas no significant influence by perceived crit- icism, self-worth, or the general tendency to ruminate was found. Emotional awareness seemed to account for some of the variance in positive mood state changes. These findings point to the mportance of adolescent self-perception (and emotional aware- ness) in dealing with parental criticism.
Keywords: Adolescents; Emotional awareness; Parental criticism; Perceived criticism; Ruminative coping; Self-worth.

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- Leo Chen, MBBS, MPsych, PhD, FRANZCP, Deborah C. W. Klooster, PhD, Martin Tik, MSc, PhD, Elizabeth H. X. Thomas, PhD, Jonathan Downar, MD, PhD, FRCPC,
Paul B. Fitzgerald, MBBS, MPM, PhD, FRANZCP, Nolan R. Williams, MD, and Chris Baeken, MD, PhD
Accelerated Repetitive Transcranial Magnetic Stimulation to Treat Major Depression: The Past, Present, and Future
Harv Rev Psychiatry (IF: 3.73; **Q2**), 2023 May-Jun;31(3):142-161., doi: 10.1097/HRP.0000000000000364.

Abstract
Repetitive transcranial magnetic stimulation (rTMS) is an effective and evidence-based therapy for treatment-resistant major depressive disorder. A conventional course of rTMS applies 20-30 daily sessions over 4-6 weeks. The schedule of rTMS delivery can be accelerated by applying multiple stimulation sessions per day, which reduces the duration of a treatment course with a predefined number of sessions. Accelerated rTMS reduces time demands, improves clinical efficiency, and potentially induces faster onset of antidepressant effects. However, considerable heterogeneity exists across study designs. Stimulation protocols vary in parameters such as the stimulation target, frequency, intensity, number of pulses applied per session or over a course of treatment, and duration of intersession intervals. In this article, clinician-researchers and neuroscientists who have extensive research experience in accelerated rTMS synthesize a consensus based on two decades of investigation and development, from early studies ("Past") to contemporaneous theta burst stimulation, a time-efficient form of rTMS gaining acceptance in clinical settings ("Present"). We propose descriptive nomenclature for accelerated rTMS, recommend avenues to optimize therapeutic and efficiency potential, and suggest using neuroimaging and electrophysiological biomarkers to individualize treatment protocols ("Future"). Overall, empirical studies show that accelerated rTMS protocols are well tolerated and not associated with serious adverse effects. Importantly, the antidepressant efficacy of accelerated rTMS appears comparable to conventional, once daily rTMS protocols. Whether accelerated rTMS induces antidepressant effects more quickly remains uncertain. On present evidence, treatment protocols incorporating high pulse dose and multiple treatments per day show promise and improved efficacy.

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- Zhixin Wang, Chris Baeken and Guo-Rong Wu
Metabolic Covariance Connectivity of Posterior Cingulate Cortex Associated with Depression Symptomatology Level in Healthy Young Adults

Abstract:
Early detection in the development of a Major Depressive Disorder (MDD) could guide earlier clinical interventions. Although MDD can begin at a younger age, most people have their first episode in young adulthood. The underlying pathophysiological mechanisms relating to such an increased risk are not clear. The posterior cingulate cortex (PCC), exhibiting high levels of brain connectivity and metabolic activity, plays a pivotal role in the pathological mechanism underlying MDD. In the current study, we used the (F-18) fluorodeoxyglucose (FDG) positron emission tomogra- phy (PET) to measure metabolic covariance connectivity of the PCC and investigated its association with depression symptomatology evaluated by the Centre for

Epidemiological Studies Depression Inventory—Revised (CESD-R) among 27 healthy individuals aged between 18 and 23 years. A signif- icant negative correlation has been observed between CESD-R scale scores and the PCC metabolic connectivity with the anterior cingulate, medial prefrontal cortex, inferior and middle frontal gyrus, as well as the insula. Overall, our findings suggest that the neural correlates of depressive symptoma- tology in healthy young adults without a formal diagnosis involve the metabolic connectivity of the PCC. Our findings may have potential implications for early identification and intervention in people at risk of developing depression.

Keywords: posterior cingulate cortex; metabolic covariance connectivity; resting-state networks

Funding

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- Luqing Wei, Fanxi Ding, Mingliang Gong, Chris Baeken, Guo-Rong Wu
The impact of sensation seeking personality trait on acute alcohol-induced disinhibition
Drug Alcohol Depend (IF: 4.49; **Q2**), 2023 Jul 22;250:110907., doi: 10.1016/j.drugalcdep.2023.110907.

Abstract

Background: Acute alcohol-related behavioral disinhibition has been well studied. But whether individual differences in the personality trait sensation seeking affect alcohol-induced behavioral disinhibition remains uncertain.

Methods: The present study used functional near-infrared spectroscopy (fNIRS) technique and a response inhibition task (i.e., Go/No-Go) to determine the impact of the sensation seeking trait on the relationship between acute alcohol administration and inhibitory control capacity, and further investigate the neural mechanisms underlying this behavioral effect. Twenty-five high-sensation seekers and twenty-six low-sensation seekers were enrolled in this study. These participants attended two sessions: once for alcohol intake (0.5g/kg) and once for placebo intake (0g/kg).

Results: Our results showed that high-sensation seekers relative to low-sensation seekers showed a significant decrease in inhibition accuracy under alcohol versus the placebo condition. Moreover, reduced prefrontal activity following acute alcohol consumption was more pronounced in high-sensation seekers compared with low-sensation seekers.

Conclusions: These findings showed that alcohol-induced behavioral disinhibition was affected by the personality trait sensation seeking and that recruitment of the prefrontal cortex contributed to the observed behavioral effect.

Keywords: Acute alcohol; Disinhibition; Sensation seeking; fNIRS.

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- Guo-Rong Wu and Chris Baeken
The left ventrolateral prefrontal cortex as a more optimal target for accelerated rTMS treatment protocols for depression?
Brain Stimul (IF: 8.96; **Q1**), 2023 Mar-Apr;16(2):642-644, doi: 10.1016/j.brs.2023.03.009. Epub 2023 Mar 17.

No abstract

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- GuoRong Wu and Chris Baeken
Precision targeting in prediction for rTMS clinical outcome in depression: what about sgACC lateralization, metabolic connectivity, and the potential role of the cerebellum?
Eur Arch Psychiatry Clin Neurosci (IF: 5.27; **Q1**), 2023 Jun 17, doi: 10.1007/s00406-023-01637-3.

Abstract
Predicting clinical response to repetitive transcranial magnetic stimulation (rTMS) in medication-resistant depression (MRD) has gained great importance in recent years. Mainly, the right subgenual anterior cingulate cortex (sgACC) functional con- nectivity has been put forward as biomarker in relation to rTMS clinical outcome. Even though the left and right sgACC may have different neurobiological functions, little is known about the possible lateralized predictive role of the sgACC in rTMS clinical outcome. In 43 right-handed antidepressant-free MRD patients, we applied a searchlight-based interregional covariance connectivity approach using the baseline ^{18}FDG-PET scan—collected from two previous high-frequency (HF)- rTMS treatment studies delivering stimulation to the left dorsolateral prefrontal cortex (DLPFC)—and investigated whether unilateral or bilateral sgACC glucose metabolism at baseline would result in different predictive metabolic connectivity patterns. Regardless of sgACC lateralization, the weaker the sgACC seed-based baseline metabolic functional connections with the (left anterior) cerebellar areas, the significantly better the clinical outcome. However, the seed diameter seems to be crucial. Similar significant findings on sgACC metabolic connectivity with the left anterior cerebellum, also unrelated to sgACC lateralization, in relation to clinical outcome were observed when using the HCPex atlas. Although we could not substantiate that specifically right sgACC metabolic connectivity would predict HF-rTMS clinical outcome, our find- ings suggest considering the entire sgACC in functional connectivity predictions. Given that the interregional covariance connectivity results were significant only when using the Beck Depression Inventory (BDI-II) and not with the Hamilton Depression Rating Scale (HDRS), our sgACC metabolic connectivity observations also suggest the possible involvement of the (left) anterior cerebellum involved in higher-order cognitive processing as part of this predictive value.
Keywords: Major depression disorder · ^{18}FDG-PET · sgACC · Covariance analysis · HF-rTMS treatment

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62271415, 61876156). This work was also supported by the Queen Elisabeth Medical Foundation for Neurosciences, by the Ghent University Multidisciplinary Research Partnership “The integrative neuroscience of behavioral con- trol”, a Grant BOF16/GOA/017 for a Concerted Research Action of Ghent University, 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) and FWO project G011018N.

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KU Leuven – UAntwerpen

Prof. dr. An Goris (KU Leuven)
Department of Neurosciences
Laboratory for Neuroimmunology
T +32 16 33 07 72
an.goris@kuleuven.be

Prof. Nathalie Cools (UAntwerpen)
Laboratory for Experimental Hematology
University of Antwerp
nathalie.cools@uza.be

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- Janssens I, Campillo-Davo D, Van den Bos J, De Reu H, Berneman ZN, Wens I, Cools N (2022) ***Engineering of regulatory T cells by means of mRNA electroporation in a GMP-compliant manner***.
Cytotherapy; IF: 5.41; **Q2**) 2022 Jun;24(6):659-672. doi: 10.1016/j.jcyt.2022.01.001. Epub 2022 Feb 20.

Abstract

Regulatory T cells (Tregs) are crucial in inducing and maintaining tolerance. This unique capacity of Tregs, in combination with proof-of-principle in preclinical studies, highlights the potential clinical use of Tregs for the treatment of autoimmunity and transplant rejection. Although proven to be safe and well tolerated in the first clinical trials, only modest clinical results were observed. In this regard, it has been hypothesized that current challenges lie in the development of antigen-specific Tregs. Here, we present an innovative, good manufacturing practices (GMP)-compliant manufacturing protocol for Tregs applicable in a clinical-grade setting, allowing efficient and safe redirection of Treg specificity. First, a soluble polymer conjugated with antibodies to CD3 and CD28 and high amounts of exogenous IL-2 for *in vitro* Treg expansion resulted in a >70-fold and 185-fold increase of a pure population of $CD4^+CD127^-CD25^{hi}$ Tregs and $CD4^+CD127^-CD25^+CD45RA^+$ Tregs, respectively. Next, as a proof-of-principle, expanded Tregs were engineered by means of TCR-encoding mRNA electroporation to generate antigen-specific Tregs. This resulted in an expression of the newly introduced TCR in up to 85% of Tregs. Moreover, we did not observe a negative effect on the phenotype of Tregs, as demonstrated by the expression of FOXP3, Helios, CTLA-4 and CCR4, nor on the TSDR methylation status. Importantly, mRNA-engineered Tregs were still able to induce *in vitro* suppression of effector T cells and produced anti-inflammatory, but not pro-inflammatory, cytokines when activated. In conclusion, our findings demonstrate that high numbers of stable and functional Tregs can be obtained with high purity and successfully engineered for gain of function, in a GMP-compliant manner. We envisage that this clinical-grade protocol will provide solid basis for future clinical application of mRNA-engineered Tregs.

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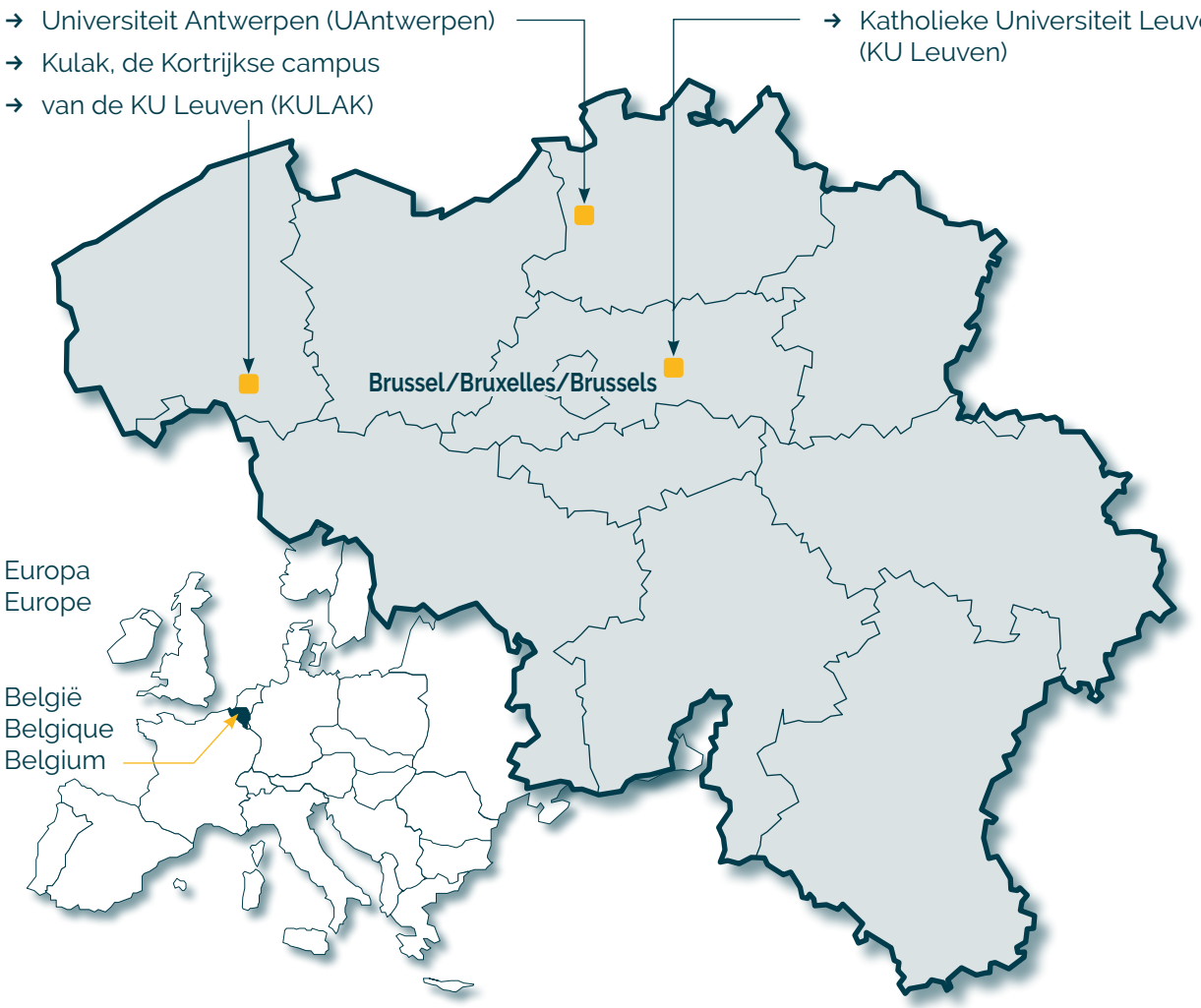

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Fondation Médicale Reine Elisabeth
Königin-Elisabeth-Stiftung für Medizin
Queen Elisabeth Medical Foundation

Publicaties – Publications – Publikationen – Publications

KU Leuven

Prof. dr. ir. Simon De Meyer
Dept. of Cardiovascular Sciences
Laboratory for Thrombosis Research
KU Leuven Campus Kulak Kortrijk
E. Sabbelaan 53
8500 Kortrijk
Belgium
Tel: +32 56 246232
simon.demeyer@kuleuven.be
www.kuleuven-kulak.be/irf/thrombosis

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- Oskar Aspegren [1] Senna Staessens Sarah Vandelanotte Linda Desender Charlotte Cordonnier , Laurent Puy Nicolas Bricout Simon F De Meyer Tommy Andersson Fabian Arnberg
Unusual Histopathological Findings in Mechanically Removed Stroke Thrombi - A Multicenter Experience.
Front Neurol (IF: 4; **Q2**) 2022 May 17;13:846293. doi: 10.3389/fneur.2022.846293. eCollection 2022.

Abstract
Background: Several studies have investigated the histopathology of mechanically retrieved thrombi from stroke patients. Thrombi with unusual components constitute about 1-2% of all stroke thrombi in clinical practice. Knowledge about these rare components is limited.
Objectives: To characterize the histopathology of unusual stroke thrombi from a real-world setting with relation to clinical presentation, patient characteristics and procedural aspects of mechanical thrombectomy.
Methods: One-thousand and eight thrombi retrieved from stroke patients with mechanical thrombectomy at three different hospitals were retrospectively reviewed for unusual histological components. Fifteen thrombi were included in the study for further histopathological analysis. Clinical data and data on procedural aspects were collected.
Results: We identified six cases with large amounts of extracellular DNA, of which three were calcified. All six cases except one received anticoagulant therapy. We describe two types of calcifications that differ with respect to general calcification morphology, von Kossa staining pattern, macrophage immunophenotype and presence of multinucleated giant cells. Cholesterol-rich (n = 3), adipocyte-like pattern-rich (n = 2), collagen-rich (n = 2) and myxomatous (n = 1) thrombi were also identified and are discussed with regard to pathogenesis and clinical and intervention characteristics. Finally, a thrombus with parts of a vascular wall is described. Suggestions for future studies are made and clinical and technical aspects of the management for these rare but important patients are discussed.
Conclusion: In our retrospective multicenter study, we characterized stroke thrombi histopathologically and found subgroups of thrombi defined by presence of rarely seen components. These defined subgroups showed relation to underlying cardiovascular disease, patient characteristics, and mechanical thrombectomy technique. Knowledge about these components may increase our understanding of stroke pathophysiology and influence interventional procedures.

Keywords: adipocyte-like; calcification; collagen; extracellular DNA; ischemic stroke; mechanical thrombectomy; myofibroblast; myxomatous.

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- Dewilde M, Desender L, Tersteeg C, Vanhoorelbeke K, De Meyer SF,
Spatiotemporal profile of neutrophil extracellular trap formation in a mouse model of ischemic stroke,
Research and practice in thrombosis and haemostasis, 2023 – Impact factor: 5.95. Dec 23;7(1):100028. doi: 10.1016/j.rpth.2022.100028. eCollection 2023 Jan.

Abstract
Background: Thromboinflammatory processes modulate the complex pathophysiology of cerebral ischemia-reperfusion (I/R) injury in ischemic stroke, but the exact underlying mechanisms remain poorly understood. Emerging evidence indicates that neutrophil extracellular traps (NETs) might play an important role in the thromboinflammatory cascade. In addition, the link between von Willebrand factor (VWF) and neutrophil recruitment in the ischemic brain might promote thromboinflammation, possibly by the formation of NETs.
Objectives: To study NET formation in a murine model of cerebral I/R injury in ischemic stroke.
Methods: The filament-induced transient middle cerebral artery occlusion model was used to induce 60 minutes of focal cerebral ischemia after which reperfusion was allowed. At different time points postischemia, NETs were identified in the ischemic mouse brain using quantitative immunofluorescence microscopy.
Results: NETs could be identified in the ipsilateral brain hemisphere. Interestingly, NETs could already be detected at 6 hours poststroke. Their presence increased at 12 hours, was highest at 24 hours, and decreased again 48 hours postischemia. Remarkably, NETs were predominantly localized within the brain vasculature postischemia, suggesting that NETs play a role in secondary microthrombosis. Strikingly, NET formation was significantly decreased in VWF-deficient mice compared to littermate wild-type mice 24 hours postischemia, indicating a possible role for VWF in promoting NETosis in the ischemic brain.
Conclusion: This study identified the spatiotemporal profile of NET formation in a mouse model of cerebral I/R injury in ischemic stroke. NETs, potentially in combination with VWF, might be attractive targets for the development of novel therapeutic strategies in ischemic stroke treatment.
Keywords: Extracellular traps; ischemic stroke; reperfusion injury; thromboinflammation; von willebrand factor.

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Thrombus formation during ECMO: Insights from a detailed histological analysis of thrombus composition.
Journal of thrombosis and haemostasis, 20 (9), 2058-2069. (Impact factor: 16.04)

Abstract
Objectives: Intra-device thrombosis remains one of the most common complications during extracorporeal membrane oxygenation (ECMO). Despite anticoagulation, approximately 35% of patients develop thrombi in the membrane oxygenator, pump heads, or tubing. The aim of this

study was to describe the molecular and cellular features of ECMO thrombi and to study the main drivers of thrombus formation at different sites in the ECMO circuits.
Approach and results: Thrombi (n = 85) were collected immediately after veno-arterial-(VA)-ECMO circuit removal from 25 patients: 23 thrombi from the pump, 25 from the oxygenator, and 37 from the tubing. Quantitative histological analysis was performed for the amount of red blood cells (RBCs), platelets, fibrin, von Willebrand factor (VWF), leukocytes, and citrullinated histone H3 (H3Cit). ECMO thrombi consist of a heterogenous composition with fibrin and VWF being the major thrombus components. A clustering analysis of the four major histological parameters identified two typical thrombus types: RBC-rich and RBC-poor/fibrin-rich thromwwbi with no significant differences in VWF and platelet content. Thrombus composition was not associated with the thrombus location, except for higher amounts of H3Cit that were found in pump and oxygenator thrombi compared to tubing samples. We observed higher blood leukocyte count and lactate dehydrogenase levels in patients with fibrin-rich thrombi.
Conclusion: We found that thrombus composition is heterogenous, independent of their location, consisting of two types: RBC-rich and a fibrin-rich types. We also found that NETs play a minor role. These findings are important to improve current anticoagulation strategies in ECMO.
Keywords: ECMO; NETs; fibrin; histology; thrombosis; thrombus composition.

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- De Meyer, S.F., Langhauser, F., Haupeltshofer, S., Kleinschnitz, C., Casas, A. with Casas, A. (corresp. author) (2022).
Thromboinflammation in Brain Ischemia: Recent Updates and Future Perspectives.
STROKE, 53 (5), 1487-1499. (Impact factor: 10.17)

Abstract
Background: Thromboinflammatory processes modulate the complex pathophysiology of cerebral ischemia-reperfusion (I/R) injury in ischemic stroke, but the exact underlying mechanisms remain poorly understood. Emerging evidence indicates that neutrophil extracellular traps (NETs) might play an important role in the thromboinflammatory cascade. In addition, the link between von Willebrand factor (VWF) and neutrophil recruitment in the ischemic brain might promote thromboinflammation, possibly by the formation of NETs.
Objectives: To study NET formation in a murine model of cerebral I/R injury in ischemic stroke.
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Results: NETs could be identified in the ipsilateral brain hemisphere. Interestingly, NETs could already be detected at 6 hours poststroke. Their presence increased at 12 hours, was highest at 24 hours, and decreased again 48 hours postischemia. Remarkably, NETs were predominantly localized within the brain vasculature postischemia, suggesting that NETs play a role in secondary microthrombosis. Strikingly, NET formation was significantly decreased in VWF–deficient mice compared to littermate wild-type mice 24 hours postischemia, indicating a possible role for VWF in promoting NETosis in the ischemic brain

Conclusion: This study identified the spatiotemporal profile of NET formation in a mouse model of cerebral I/R injury in ischemic stroke. NETs, potentially in combination with VWF, might be attractive targets for the development of novel therapeutic strategies in ischemic stroke treatment.
Keywords: Extracellular traps, ischemic stroke, reperfusion injury, thromboinflammation, von willebrand factor

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Prof Lieve Moons
Head Division Animal Physiology and Neurobiology (APN)
Head RU Neural Circuit Development and Regeneration (http://bio.kuleuven.be/df/LM/)
Department of Biology, KU Leuven Zoological Institute, Naamsestraat 61, bus 2464
Department of Biology, KU Leuven Zoological Institute, Naamsestraat 61, bus 2424
3000- Leuven

Lies De Groef, MSc, PhD
Onderzoeksgroep neurale ontwikkeling en regeneratie premonstreit college
Naamsestraat 61 bus 2464 b
3000 Leuven

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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
pierre.vanderhaeghen@kuleuven.be

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- Vanderhaeghen P, Franck Polleux.
Developmental mechanisms underlying the evolution of human cortical circuits.
Nature Rev. Neurosci. 2023, *IF: 39* - Nat Rev Neurosci. 2023 Apr; 24(4): 213–232.
Published online 2023 Feb 15. doi: **10.1038/s41583-023-00675-z**

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.

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Mitochondria Metabolism Sets the Species-Specific Tempo of Neuronal Development.
Science (2023) 379, eabn4705 DOI: 10.1126/science.abn4705. IF: 47.73 Q1

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.

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CROCCP2 acts as a human:specific modifier of cilia dynamics and mTOR signalling to promote expansion of cortical progenitors
Neuron Neuron (IF: 17.17; **Q1**)2023 Jan 4;111(1):65-80.e6.doi: 10.1016/j.neuron.2022.10.018. *(2022):S0896-6273(22)00947-3. IF: 18 – Q1*

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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- Vermaercke B, Bonin V, **Vanderhaeghen P.**
Studying human neural function in vivo at the cellular level: Chasing chimeras?
Cell (2022) 185(26): 4869-4872. *IF: 41.58 - Q1*

Abstract
Despite its importance to understanding human brain (dys)function, it has remained challenging to study human neurons in vivo. Recent approaches, using transplantation of human cortical neurons into the rodent brain, offer new prospects for the study of human neural function and disease in vivo, from molecular to circuit levels.

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

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Gain-of-function variants in the ion channel gene TRPM3 underlie spectrum of neurodevelopmental disorders.
Elife 12. https://doi.org/10.7554/eLife.81032 IF 8.14 Q1

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.

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- DeBruyn,H.,Corthout,N.,Munck,S.,Everaerts,W.,Voets,T.,2022.
Machine learning-assisted fluoroscopy of bladder function in awake mice.
Elife 11. https://doi.org/10.7554/eLife.79378 - IF 8.14 -Q1

Abstract
Understanding the lower urinary tract (LUT) and development of highly needed novel therapies to treat LUT disorders depends on accurate techniques to monitor LUT (dys)function in preclinical models. We recently developed videocystometry in rodents, which combines intravesical pressure measurements with X-ray-based fluoroscopy of the LUT, allowing the in vivo analysis of the process of urine storage and voiding with unprecedented detail. Videocystometry relies on the precise contrast-based determination of the bladder volume at high temporal resolution,

which can readily be achieved in anesthetized or otherwise motion-restricted mice but not in awake and freely moving animals. To overcome this limitation, we developed a machine-learning method, in which we trained a neural network to automatically detect the bladder in fluoroscopic images, allowing the automatic analysis of bladder filling and voiding cycles based on large sets of time-lapse fluoroscopic images (>3 hr at 30 images/s) from behaving mice and in a noninvasive manner. With this approach, we found that urethane, an injectable anesthetic that is commonly used in preclinical urological research, has a profound, dose-dependent effect on urethral relaxation and voiding duration. Moreover, both in awake and in anesthetized mice, the bladder capacity was decreased ~fourfold when cystometry was performed acutely after surgical implantation of a suprapubic catheter. Our findings provide a paradigm for the noninvasive, in vivo monitoring of a hollow organ in behaving animals and pinpoint important limitations of the current gold standard techniques to study the LUT in mice.

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- Held, K., Aloi, V.D., Freitas, A.C.N., Janssens, A., Segal, A., Przibilla, J., Philipp, S.E., Wang, Y.T., Voets, T., Vriens, J., 2022.
Pharmacological properties of TRPM3 isoforms are determined by the length of the pore loop.
Br J Pharmacol 179, 3560-3575. https://doi.org/10.1111/bph.15223 - 8.74 – Q1

Abstract
Background and purpose: Transient receptor potential melastatin 3 (TRPM3) is a non-selective cation channel that plays a pivotal role in the peripheral nervous system as a transducer of painful heat signals. Alternative splicing gives rise to several TRPM3 variants. The functional consequences of these splice isoforms are poorly understood. Here, the pharmacological properties of TRPM3 variants arising from alternative splicing in the pore-forming region were compared.
Experimental approach: Calcium microfluorimetry and patch clamp recordings were used to compare the properties of heterologously expressed TRPM31 (long pore variant) and TRPM32-6 (short pore variants). Furthermore, site-directed mutagenesis was done to investigate the influence of the length of the pore loop on the channel function.
Key results: All short pore loop TRPM3 variants (TRPM32-6) were activated by the neurosteroid pregnenolone sulphate (PS) and by nifedipine, whereas the long pore loop variant TRPM31 was insensitive to either compound. In contrast, TRPM31 was robustly activated by clotrimazole, a compound that does not directly activate the short pore variants but potentiates their responses to PS. Clotrimazole-activated TRPM31 currents were largely insensitive to established TRPM32 antagonists and were only partially inhibited upon activation of the μ opioid receptor. Finally, by creating a set of mutant channels with pore loops of intermediate length, we showed that the length of the pore loop dictates differential channel activation by PS and clotrimazole.
Conclusion and implications: Alternative splicing in the pore-forming region of TRPM3 defines the channel's pharmacological properties, which depend critically on the length of the pore-forming loop.
Linked articles: This article is part of a themed issue on Structure Guided Pharmacology of Membrane Proteins (BJP 75th Anniversary). To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v179.14/issuetoc.

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Endometrium, Endometriosis and Reproduction at the KU Leuven for their helpful discussions and comments. This project has received funding from the Belgian Federal Government (IUAP P7/13 to T.V.), the Research Foundation–Flanders (G.0565.07 and G.0825.11 to T.V. and J.V.; G.084515N and G.0B1819N to J.V.), the Research Council of the KU Leuven (C1TRPLe to T.V.), the Queen Elisabeth Medical Foundation for Neurosciences (to T.V.), the Belgian Foundation Against Cancer (to J.V. and T.V.) and the Saarland University (HOMFOR) (to S.E.P.). The manuscript was published with support of the University Foundation from Belgium (WA0292 to K.H.). K.H. is a "postdoctoral fellow" of the Research Foundation–Flanders, Belgium and a research trainee of the Michael Smith Foundation for Health Research/Vancouver Coastal Health Research Institute/VGH and UBC Hospital Foundation.

- 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 - IF 4.43 Q2

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 IC_{50} values between 2 and 10 μM. 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 μM, 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.

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

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UAntwerpen

Prof. dr. Sarah Weckhuysen, MD, PhD
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
Belgium
www.uza.be/neurologie

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***KCNQ2 R144 variants cause neurodevelopmental disability with language impairment and autistic features without neonatal* seizures through a gain-of-function mechanism.**
EBioMedicine. 2022 Jul;81:104130. doi: 10.1016/j.ebiom.2022.104130. PMID: 35780567, IF (2021) = 11.205, Q-index = Q1, IF percentile = 90.29 (Medicine, Research & Experimental)

Abstract
Background Prior studies have revealed remarkable phenotypic heterogeneity in KCNQ2-related disorders, corre- lated with effects on biophysical features of heterologously expressed channels. Here, we assessed phenotypes and functional properties associated with KCNQ2 missense variants R144W, R144Q, and R144G. We also explored *in vitro* blockade of channels carrying R144Q mutant subunits by amitriptyline.
Methods Patients were identified using the RIKEE database and through clinical collaborators. Phenotypes were col- lected by a standardized questionnaire. Functional and pharmacological properties of variant subunits were analyzed by whole-cell patch-clamp recordings.
Findings Detailed clinical information on fifteen patients (14 novel and 1 previously published) was analyzed. All patients had developmental delay with prominent language impairment. R144Q patients were more severely affected than R144W patients. Infantile to childhood onset epilepsy occurred in 40%, while 67% of sleep-EEGs showed sleep-activated epileptiform activity. Ten patients (67%) showed autistic features. Activation gating of homo- meric Kv7.2 R144W/Q/G channels was left-shifted, suggesting gain-of-function effects. Amitriptyline blocked chan- nels containing Kv7.2 and Kv7.2 R144Q subunits.
Interpretation Patients carrying KCNQ2 R144 gain-of-function variants have developmental delay with prominent language impairment, autistic features, often accompanied by infantile- to childhood-onset epilepsy and EEG sleep- activated epileptiform activity. The absence of neonatal seizures is a robust and important clinical differentiator between KCNQ2 gain-of-function and loss-of-function variants. The Kv7.2/7.3 channel blocker amitriptyline might represent a targeted treatment.

Keywords: KCNQ2; Gain-of-function; Amitriptyline; Autism; Developmental and epileptic encephalopathy

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- Weuring Wout J., Dirkx N, De Vriendt E, Smal N, van de Vondervoort J, van 'Slot Ruben, Koetsier M , Weckhuysen S, Koeleman Bobby PC
Efficient and accurate prime editing strategy to correct genetic alterations in hiPSC using single EF-1alpha driven all-in-one plasmid
https://www.biorxiv.org/content/10.1101/2022.05.04.490422v2.full.pdf.

Abstract
Prime editing (PE) is currently the most effective and versatile technology to make targeted alterations in the genome. Several improvements to the PE machinery have recently been made, and have been tested in a range of model systems, including immortalized cell lines, stem-cells and animal models. While nick RNA (ncRNA)-dependent PE systems like PE3 and PE5 are currently considered to be the most effective, they come with undesired indels or SNVs at the edit locus. Here, we aimed to improve ncRNA-independent systems PE2 and PE4max by generating novel all-in-one (pAIO) plasmids, driven by a tissue-broad EF-1alpha promoter, that is especially suitable for human iPSC models, and linked to a GFP tag for fluorescent based sorting. These novel pAIO systems effectively corrected mutations observed in patients suffering from epileptic encephalopathy, including a truncating SCN1A R612* variant in HEK293T cells and a gain-of-function KCNQ2 R201C variant in patient-derived hiPSC, with edit efficiency up to 50%. We also show that introducing additional silent PAM-removing mutations can negatively influence edit efficiency. Finally, we observed an absence of genome-wide PE off-target effects at pegRNA homology sites. Taken together, our study shows an improved efficacy and accuracy f EF-1alpha driven ncRNA-independent pAIO PE plasmids in hiPSC.

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- Dirkx N, Weuring WJ, De Vriendt E, Smal N, van de Vondervoort J, van 't Slot R, Koetsier M, Zonnekein N, De Pooter T, Weckhuysen S, Koeleman BPC.
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. PMID: 37443005; PMCID: PMC10347817
IF (2023) = 5.4, Q-index = Q1, IF percentile = 84.2 (Biology)

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 includ- ing 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 popula- tion 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 effi- cient 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-1alfa, Human-induced pluripotent stem cells, Gene editing, Monogenic diseases

Funding
This work was funded by Vrienden WKZ fund 1616091 (MING). SW received funding from FWO (1861419N and G041821N), European Joint Programme on Rare Disease JTC 2020 (TreatKCNQ), and the Queen Elisabeth Medical Foundation. ND receives support from FWO-SB (1S59221N).

- Millevert C, Weckhuysen S; ILAE Genetics Commission.
***ILAE Genetic Literacy Series: Self-limited familial epilepsy syndromes with onset in neonatal age and infancy*.**
Epileptic Disord. 2023 Aug;25(4):445-453. doi: 10.1002/epd2.20026. Epub 2023 Jun 22. PMID: 36939707
IF (2023) = 2.3, Q-index = Q3, IF percentile = 29.0 (Clinical Neurology)
Abstract
The self-limited (familial) epilepsies with onset in neonates or infants, formerly called benign familial neonatal and/or infantile epilepsies, are autosomal dominant disorders characterized by neonatal- or infantile-onset focal motor seizures and the absence of neurodevelopmental complications. Seizures tend to remit during infancy or early childhood and are therefore called "self-limited". A positive family history for epilepsy usually suggests the genetic etiology, but incomplete penetrance and de novo inheritance occur. Here, we review the phenotypic spectrum and the genetic architecture of self-limited (familial) epilepsies with onset in neonates or infants. Using an illustrative case study, we describe important clues in recognition of these syndromes, diagnostic steps including genetic testing, management, and genetic counseling.
Keywords: KCNQ2; KCNQ3; PRRT2; SCN2A; SCN8A; self-limited familial epilepsy.

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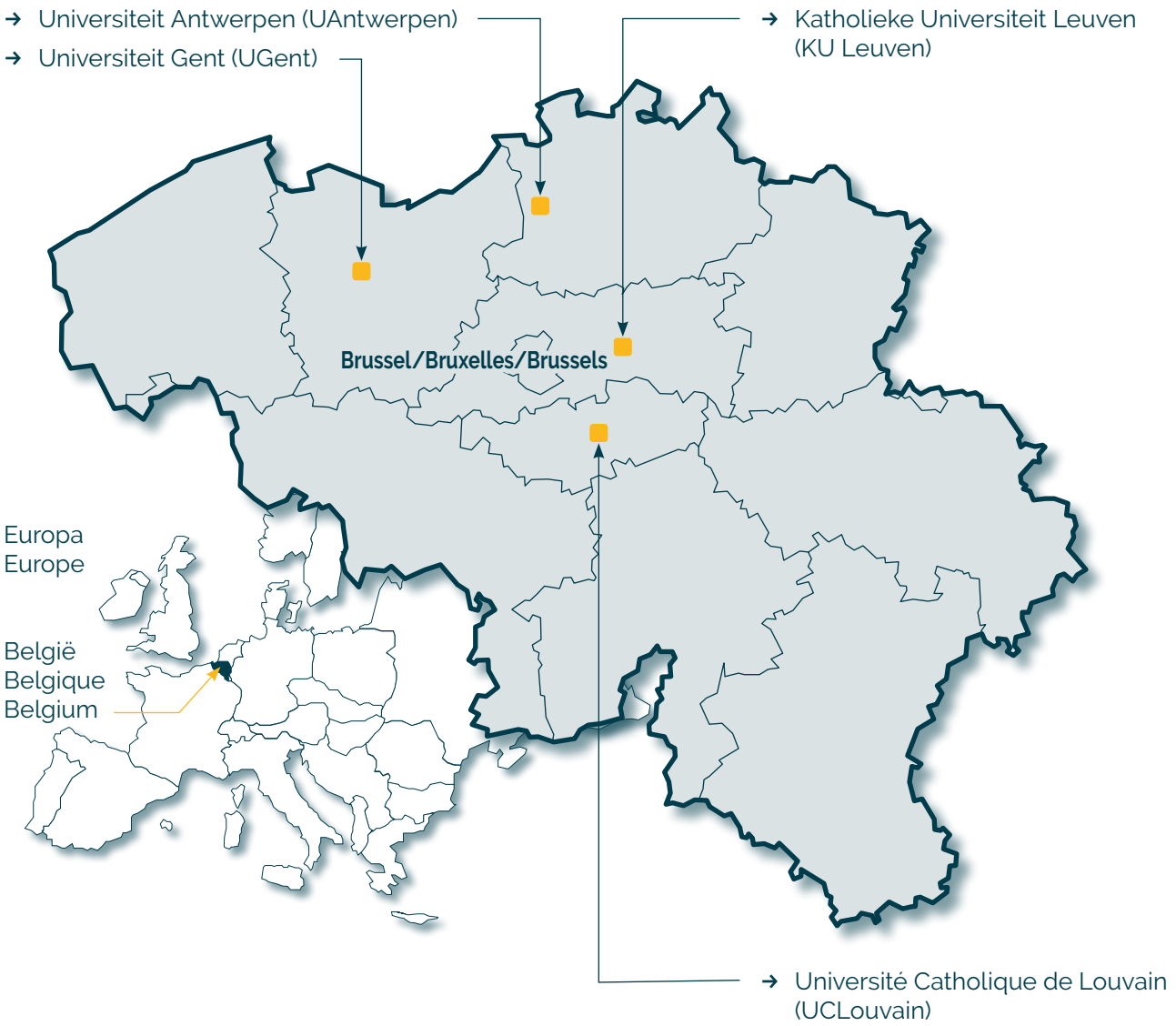

Geneeskundige Stichting Koningin Elisabeth
Fondation Médicale Reine Elisabeth
Königin-Elisabeth-Stiftung für Medizin
Queen Elisabeth Medical Foundation

Publicaties – Publications – Publikationen – Publications

UGent

Prof. dr. Evelien Carrette
Beleidsmedewerker Neurologie
Neuroscience@U(Z)Gent

Universitair Ziekenhuis Gent
C. Heymanslaan 10
9000 Gent
T +32 9 332 45 40
evelien.carrette@uzgent.be
Skype eveliencarrette
Ingang 12
Route 1556
uzgent.be

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- Gadeyne S, Mertens A, Carrette E, Van den Bossche F, Boon P, Raedt R, Vonck K (2021).
  ***Transcutaneous auricular* vagus nerve stimulation cannot modulate the P3b event-related potential in healthy volunteers.**
  Clin Neurophysiol. 2022. 135:22-29(IF 3,7) https://doi.org/10.1016/j.clinph.2021.11.079

Abstract

Objective: The release of cortical norepinephrine is one of the possible mechanisms of action of vagus nerve stimulation (VNS), a neuromodulatory treatment currently under investigation for cognitive impairment. Transcutaneous auricular VNS (taVNS) may be able to activate vagal nerve branches ending in the brainstem's locus coeruleus (LC) non-invasively. The aim was to investigate if acute taVNS can modulate the P3b, a cognitive event-related potential (ERP) reflecting noradrenergic brain activation under control of the LC.

Methods: Thirty-nine healthy volunteers performed an auditory oddball task during no stimulation, sham stimulation and taVNS in a randomized order. P3b amplitude, latency and behavioral outcome parame- ters were compared between conditions using linear mixed models.

Results: P3b amplitude and latency during taVNS did not differ significantly from sham or control. Reaction time shortened and P3b latency prolonged with repetition of the oddball task.

Conclusions: We were unable to modulate cognitive ERPs by means of acute taVNS in a large group of healthy volunteers.

Significance:: Targeting vagal nerve fibres via a transcutaneous approach did not alter the P3b in healthy participants. The stimulation parameters used and transient delivery of taVNS might be insufficient to adequately modulate the LC. Also, a disbalanced locus coeruleus - norepinephrine system in patients may be more prone for improvement.

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- Poppa T, Benschop L, Horczak P, Vanderhasselt MA, Carrette E, Bechara A, Baeken C, Vonck K.
  Auricular transcutaneous vagus nerve stimulation modulates the heart-evoked potential.
  Brain Stimul. 2022. 15(1):260-269. (IF 8,9) .

Abstract

Background: There is active interest in biomarker discovery for transcutaneous auricular vagus nerve stimulation (taVNS). However, greater understanding of the neurobiological mechanisms is needed to identify candidate markers. Accumulating evidence suggests that taVNS influences activity in solitary and parabrachial nuclei, the primary brainstem relays for

the transmission of visceral sensory afferents to the insula. The insula mediates interoception, which concerns the representation and regulation of homeostatic bodily states. Consequently, interoceptive pathways may be relevant to taVNS mechanisms of action.
Hypotheses: We hypothesized that taVNS would modulate an EEG-derived marker of interoceptive processing known as the heart-evoked potential (HEP). We also hypothesized that taVNS-induced HEP effects would be localizable to the insula.
Methods: Using a within-subject, sham-controlled design, we recorded EEG and ECG concurrent to taVNS in 43 healthy adults. Using ECG and EEG data, we extracted HEPs. Estimation of the cortical sources of the taVNS-dependent HEP responses observed at the scalp were computed using the Boundary Element Method and weighted Minimum Norm Estimation. Statistics were calculated using cluster-based permutation methods.
Results: taVNS altered HEP amplitudes at frontocentral and centroparietal electrode sites at various la- tencies. The taVNS-dependent HEP effect was localized to the insula, operculum, somatosensory cortex, and orbital and ventromedial prefrontal regions.
Conclusion: The results support the hypothesis that taVNS can access the insula as well as functionally and anatomically connected brain regions. HEPs may serve as an objective, non-invasive outcome parameter for the cortical effects of taVNS.

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- Mertens A, Gadeyne S, Lescrauwaet E, Carrette E, Meurs A, De Herdt V, Dewaele F, Raedt R, Miatton M, Boon P, Vonck K (2022).
The potential of invasive and non-invasive vagus nerve stimulation to improve verbal memory performance in epilepsy patients.
Scientific Reports 2022. 12(1):1984

Abstract
It has been demonstrated that acute vagus nerve stimulation (VNS) improves word recognition memory in epilepsy patients. Transcutaneous auricular vagus nerve stimulation (taVNS) has gained interest as a noninvasive alternative to improve cognition. In this prospective randomized crossover study, we investigated the effect of both invasive VNS and taVNS on verbal memory performance in 15 patients with drugresistant epilepsy. All patients conducted a word recognition memory paradigm in 3 conditions: VNS ON, VNS OFF and taVNS (3period 3treatment crossover study design). For
each condition, patients memorized 21 highlighted words from text paragraphs. Afterwards, the intervention was delivered for 30 s. Immediate recall and delayed recognition scores were obtained
for each condition. This memory paradigm was repeated after 6 weeks of VNS therapy in 2 conditions: VNS ON and VNS OFF (2period 2treatment crossover study design). Acute VNS and taVNS did
not improve verbal memory performance. Immediate recall and delayed recognition scores were significantly improved after 6 weeks of VNS treatment irrespective of the acute intervention. We can conclude that the previously described positive effects of invasive VNS

on verbal memory performance could not be replicated with invasive VNS and taVNS. An improved verbal memory performance was seen after 6 weeks of VNS treatment, suggesting that longer and more repetitive stimulation of the vagal pathway is required to modulate verbal memory performance.

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- Bouckaert C, Raedt R, Larsen LE, El Tahry R, Gadeyne S, Carrette E, Proesmans S, Dewaele F, Delbeke J, De Herdt V, Meurs A, Mertens A, Boon P, Vonck K. Laryngeal
Muscle-Evoked Potential Recording as an Indicator of Vagal Nerve Fiber Activation.
Neuromodulation. 2022 Apr;25(3):461-470. doi: 10.1016/j.neurom.2022.01.014. Epub 2022 Feb 15. PMID: 35177376.

Abstract
Background: Vagus nerve stimulation (VNS) is an adjunctive therapy for drug-resistant epilepsy. Noninvasive evoked potential recordings in laryngeal muscles (LMEPs) innervated by vagal branches may provide a marker to assess effective vagal nerve fiber activation. We investigated VNS-induced LMEPs in patients with epilepsy in acute and chronic settings.
Materials and methods: A total of 17 of 25 patients underwent LMEP recordings at initiation of therapy (acute group); 15 of 25 patients after one year of VNS (chronic group); and 7 of 25 patients were tested at both time points (acute + chronic group). VNS-induced LMEPs were recorded following different pulse widths and output currents using six surface laryngeal EMG electrodes to calculate input/output curves and estimate LMEP latency, threshold current for minimal ($I_{threshold}$), half-maximal (I_{50}), and 95% of maximal (I_{95}) response induction and amplitude of maximal response (V_{max}). These were compared with the acute + chronic group and between responders and nonresponders in the acute and chronic group.
Results: VNS-induced LMEPs were present in all patients. $I_{threshold}$ and I_{95} values ranged from 0.25 to 1.00 mA and from 0.42 to 1.77 mA, respectively. Estimated mean LMEP latencies were 10 ± 0.1 milliseconds. No significant differences between responders and nonresponders were observed. In the acute + chronic group, $I_{threshold}$ values remained stable over time. However, at the individual level in this group, V_{max} was lower in all patients after one year compared with baseline.
Conclusions: Noninvasive VNS-induced LMEP recording is feasible both at initiation of VNS therapy and after one year. Low output currents (0.25-1.00 mA) may be sufficient to activate vagal A-motor fibers. Maximal LMEP amplitudes seemed to decrease after chronic VNS therapy in patients.
Keywords: Biomarkers; epilepsy; laryngeal muscle-evoked potentials; response; vag

Funding
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by the Fond de Recherche Clinique Cliniques Universitaires Saint-Luc. Evelien Carrette is supported by a research grant from Ghent University Hospital and Q.E.M.F.. Silke Proesmans and Kristl Vonck have been funded by the BOF-UGent special research. Paul Boon is supported by grants from the FWO Flanders, BOF-UGent, Ghent University Hospital, and E-Epilepsy (EU).

- De Smet S, Baeken C, Seminck N, Tilleman J, Carrette E, Vonck K, Vanderhasselt MA.
Non-invasive vagal nerve stimulation enhances cognitive emotion regulation.
Behav Res Ther. 2021 145 .

Abstract
Transcutaneous auricular vagus nerve stimulation (taVNS) has been proposed as a potential new tool in the treatment of major depressive disorder. Prior studies have demonstrated that taVNS enhances cognitive control and is able to modulate brain activity in key regions involved in cognitive emotion regulation, such as the anterior cingulate and medial prefrontal cortex, which is known to be impaired in depressed patients. Preclinical studies are lacking but may provide important insights into the working mechanisms of taVNS on cognitive emotion regulatory processes. In this between-subject study, 83 healthy subjects underwent a single-session of active taVNS or sham stimulation, after which cognitive reappraisal was examined using a computer-based cognitive emotion regulation task. Our results indicate that participants receiving active taVNS, compared to sham, were better at using cognitive reappraisal and rated their response to emotion-eliciting pictures as less intense. Yet, even though we found significant differences in behavioral measures of cognitive emotion regulation, no differences between groups were found in terms of physiological responses to the emotional stimuli. Overall, these findings suggest a positive effect of taVNS on the cognitive reappraisal of emotions, but future studies assessing objective measures of neural activity during cognitive emotion regulation following taVNS

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- Carrette S, Boon P, Klooster D, Van Dycke A, Carrette E, Miatton M, Raedt R, Delbeke J, Meurs A, Vonck K.
Continuous theta burst stimulation for drug-resistant epilepsy.
Front Neurosci. 2022 Aug 17;16:885905. doi: 10.3389/fnins.2022.885905. PMID: 36061598; PMCID: PMC9433314. IF 3.71 -Q1

Abstract
Introduction: Repetitive transcranial magnetic stimulation (rTMS) may have anti-epileptic effects, especially in patients with neocortical lesions. Initial clinical trials demonstrated that the duration of the seizure reducing effect is relatively short-lived. In the context of a chronic condition like epilepsy, theta burst stimulation (TBS) may represent a potential solution in optimizing treatment practicality and durability as it was demonstrated to be associated with longer-lasting after-effects. TBS has been studied extensively in diverse neuropsychiatric conditions, but a therapeutic TBS protocol has not previously been applied in epilepsy patients.
Materials and methods: We performed a prospective open-label pilot study of 4-day accelerated continuous TBS (cTBS) treatment in patients with neocortical drug-resistant epilepsy (DRE). A treatment session consisted of 5 cTBS trains, each comprising 600 pulses presented in 50 Hz

triplet bursts every 200 ms, delivered at 10-min intertrain-intervals, targeted over the epileptic focus (EF) using a neuronavigation-guided figure-of-8 coil. Safety and feasibility, and seizure frequency were assessed as primary and secondary endpoints, respectively, over a 4-week baseline period, a 1-week treatment period and a 7-week follow-up period, using adverse event logging, electro-encephalography, cognitive, and psychological questionnaires and a seizure diary kept by the patients and/or caregivers.
Results: Seven subjects (4M:3F; median age 48, interquartile ranges 25) underwent the treatment protocol. Adverse events were reported in all subjects but were mild and transient. No clinical or electrographic seizures were evoked during or immediately following stimulation. No deterioration was found in cognition nor in psycho-emotional well-being following treatment. Treatment burden was acceptable, but seems to depend on clinical effect, duration of ongoing effect and stimulation site. Median weekly seizure frequency and ratio of seizure-free weeks did not change significantly in this small patient cohort.
Conclusion: We report the results of the first ever trial of cTBS as a treatment for neocortical DRE. A 4-day accelerated cTBS protocol over the EF appears safe and feasible. Although the design and sample size of this open-label pilot study is unfit to reliably identify a therapeutic effect, results encourage further exploration of cTBS as an anti-epileptic treatment and potential optimization compared to conventional rTMS in a dedicated randomized controlled trial. (clinicaltrials.gov: NCT02635633).
Keywords: epilepsy; neurostimulation; safety; theta burst stimulation; transcranial magnetic stimulation (repetitive); treatment.

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SC was supported by an Aspirant grant from "Fonds voor Wetenschappelijk Onderzoek" (FWO) Flanders. PB was upported by grants of the FWO Flanders, BOF-UGent, Ghent University Hospital, and E-Epilepsy (EU). DK was supported by a Junior Postdoc grant from FWO Flanders. EC was supported by a research grant of Ghent University Hospital and "Geneeskundige Stichting Koningin Elisabeth" (G.S.K.E.). RR was supported by grants of the FWO Flanders and BOF-UGent special research fund. AM was supported by grants of the FWO Flanders. KV had been funded by the "Bijzonder Onderzoeks Fonds" (BOF) of Ghent University. TMS equipment was purchased using the "basic equipment fund" of the BOF. 4Brain has also received funding from the G.S.K.E. for Neuroscience.

- Charlotte Bouckaert, PhD; Robrecht Raedt, PhD; Lars Emil Larsen, PhD; Riëm El Tahry, MD, PhD;Stefanie Gadeyne, MSc; Evelien Carrette, PhD; Silke Proesmans, MSc; Frank Dewaele, MD, PhD; Jean Delbeke, MD, PhD; Veerle De Herdt, MD, PhD; Alfred Meurs, MD, PhD; Ann Mertens, MD; Paul Boon, MD, PhD; Kristl Vonck, MD, PhD
Laryngeal Muscle-Evoked Potential Recording as an Indicator of Vagal Nerve Fiber Activation
Neuromodulation, https://doi.org/10.1016/j.neurom.2022.01.014

Abstract
Background: Vagus nerve stimulation (VNS) is an adjunctive therapy for drug-resistant epilepsy. Noninvasive evoked potential recordings in laryngeal muscles (LMEPs) innervated by vagal branches may provide a marker to assess effective vagal nerve fiber activation. We investigated VNS-induced LMEPs in patients with epilepsy in acute and chronic settings.
Materials and Methods: A total of 17 of 25 patients underwent LMEP recordings at initiation of therapy (acute group); 15 of 25 patients after one year of VNS (chronic group); and 7 of 25 patients were tested at both time points (acute + chronic group). VNS-induced LMEPs were recorded following different pulse widths and output currents using six surface laryngeal EMG

elec- trodes to calculate input/output curves and estimate LMEP latency, threshold current for minimal (Ithreshold), half-maximal (I50), and 95% of maximal (I95) response induction and amplitude of maximal response (Vmax). These were compared with the acute + chronic group and between responders and nonresponders in the acute and chronic group.
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Conclusions: Noninvasive VNS-induced LMEP recording is feasible both at initiation of VNS therapy and after one year. Low output currents (0.25–1.00 mA) may be sufficient to activate vagal A-motor fibers. Maximal LMEP amplitudes seemed to decrease after chronic VNS therapy in patients.
Keywords: Biomarkers, epilepsy, laryngeal muscle-evoked potentials, response, vagus nerve stimulation

Funding
Charlotte Bouckaert and Ann Mertens are supported by an “Aspirant” grant from the “Fonds voor Wetenschappelijk Onderzoek” (FWO) Flanders. Robrecht Raedt is supported by grants from the FWO Flanders and Bijzonder Onderzoeksfonds University Gent special research fund. Lars Emil Larsen is supported by grants from FWO Flanders and the Queen Elisabeth Medical Foundation (Q.E.M.F.) for Neurosciences. Riëm El Tahry is supported by the Fond de Recherche Clinique Cliniques Universitaires Saint-Luc. Evelien Carrette is supported by a research grant from Ghent University Hospital and Q.E.M.F.. Silke Proesmans and Kristl Vonck have been funded by the BOF-UGent special research. Paul Boon is supported by grants from the FWO Flanders, BOF-UGent, Ghent University Hospital, and E

Dr. Lars Emil Larsen, PhD
Postdoctoral Researcher 4Brain/MEDISIP
Ghent University
Campus UZ
Corneel Heymanslaan 10,
Entrance 36 - Ground floor
9000 Gent
Belgium

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- Acharya AR, Larsen LE, Delbeke J, Wadman WJ, Vonck K, Meurs A, Boon P, Raedt R.
In vivo inhibition of epileptiform afterdischarges in rat hippocampus by light-activated chloride channel, stGtACR2.
CNS Neuroscience Therapeutics, *2022 Dec 8.doi: 10.1111/cns.14029.*
Impact Factor (2021, most recent) = 7.035, Category: Pharmacology & Pharmacy, Rank 31/279, Q1

Abstract
Aims: The blue light-sensitive chloride-conducting opsin, stGtACR2, provides potent optogenetic silencing of neurons. The present study investigated whether activation of stGtACR2 in granule cells of the dentate gyrus (DG) inhibits epileptic afterdischarges in a rat model.
Methods: Rats were bilaterally injected with 0.9 µl of AAV2/7-CaMKII-stGtACR2-fusionred in the DG. Three weeks later, afterdischarges were recorded from the DG by placing an optrode at the injection site and a stimulation electrode in the perforant path (PP). Afterdischarges were evoked every 10 min by unilateral electrical stimulation of the PP (20 Hz, 10 s). During every other afterdischarge, the DG was illuminated for 5 or 30 s, first ipsilaterally and then bilaterally to the PP stimulation. The line length metric of the afterdischarges was compared between illumination conditions.
Results: Ipsilateral stGtACR2 activation during afterdischarges decreased the local field potential line length only during illumination and specifically at the illuminated site but did not reduce afterdischarge duration. Bilateral illumination did not terminate the afterdischarges.
Conclusion: Optogenetic inhibition of excitatory neurons using the blue-light sensitive chloride channel stGtACR2 reduced the amplitude of electrically induced afterdischarges in the DG at the site of illumination, but this local inhibitory effect was insufficient to reduce the duration of the afterdischarge.

Keywords: GtACR2; afterdischarges; chloride; hippocampus; optogenetics; seizures.

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- Craey E, Hulpia F, Spanoghe J, Manzella S, Larsen LE, Sprengers M, De Bundel D, Smolders I, Carrette E, Delbeke J, Vonck K, Boon P, Van Calenbergh S, Wadman WJ, Raedt R.
Ex Vivo Feedback Control of Neurotransmission Using a Photocaged Adenosine A1 Receptor Agonist.
Peer Reviewed, Impact factor (2021, most recent) = 6.208, Category: Biochemistry & Molecular Biology, Rank 69/297, Q1 2022 Aug 10;23(16):8887. doi: 10.3390/ijms23168887.

Abstract
We report the design, synthesis, and validation of the novel compound photocaged N^6-cyclopentyladenosine (cCPA) to achieve precisely localized and timed release of the parent adenosine A1 receptor agonist CPA using 405 nm light. G_i protein-coupled A_1 receptors (A_1Rs)

modulate neurotransmission via pre- and post-synaptic routes. The dynamics of the CPA-mediated effect on neurotransmission, characterized by fast activation and slow recovery, make it possible to implement a closed-loop control paradigm. The strength of neurotransmission is monitored as the amplitude of stimulus-evoked local field potentials. It is used for feedback control of light to release CPA. This system makes it possible to regulate neurotransmission to a pre-defined level in acute hippocampal brain slices incubated with 3 µM cCPA. This novel approach of closed-loop photopharmacology holds therapeutic potential for fine-tuned control of neurotransmission in diseases associated with neuronal hyperexcitability.
Keywords: adenosine A1 receptor; caged compounds; hippocampus; photopharmacology.

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

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UCLouvain

Prof. Riëm El Tahry, MD, PhD
Chef de Clinique Adjointe Neurologie,
Centre de référence pour l'épilepsie réfractaire

Secrétariat:
Tel.: +32 2 764 10 82 / +32 2 764 33 09
Avenue Hippocrate 10
1200 Brussels

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- Vespa, Simone ; Stumpp, Lars ; Liberati, Giulia ; Delbeke, Jean ; Nonclercq, Antoine ; Mouraux, André ; El Tahry, Riëm.
Characterization of vagus nerve stimulation-induced pupillary responses in epileptic patients.
Brain stimulation, (2022). IF : 9, cited :0 022 Nov-Dec;15(6):1498-1507. doi: 10.1016/j.brs.2022.11.002. Epub 2022 Nov 17.

Abstract
Background: Modulation of the locus coeruleus (LC)-noradrenergic system is a key mechanism of vagus nerve stimulation (VNS). Activation of the LC produces pupil dilation, and the VNS-induced change in pupil diameter was demonstrated in animals as a possible dose-dependent biomarker for treatment titration.
Objective: This study aimed to characterize VNS-induced pupillary responses in epileptic patients.
Methods: Pupil diameter was recorded in ten epileptic patients upon four stimulation conditions: three graded levels of VNS intensity and a somatosensory control stimulation (cutaneous electrical stimulation over the left clavicle). For each block, the patients rated the intensity of stimulation on a numerical scale. We extracted the latency of the peak pupil dilation and the magnitude of the early (0-2.5 s) and late components (2.5-5 s) of the pupil dilation response (PDR).
Results: VNS elicited a peak dilation with longer latency compared to the control condition ($p = 0.043$). The magnitude of the early PDR was significantly correlated with the intensity of perception ($p = 0.046$), whereas the late PDR was not ($p = 0.19$). There was a significant main effect of the VNS level of intensity on the magnitude of the late PDR ($p = 0.01$) but not on the early PDR ($p = 0.2$). The relationship between late PDR magnitude and VNS intensity was best fit by a Gaussian model (inverted-U).
Conclusions: The late component of the PDR might reflect specific dose-dependent effects of VNS, as compared to control somatosensory stimulation. The inverted-U relationship of late PDR with VNS intensity might indicate the engagement of antagonist central mechanisms at high stimulation intensities.
Keywords: Biomarkers; Dose dependency; Drug-resistant epilepsy; Pupillometry; VNS parameters.

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- M. Dumoulin, S. Vespa, G. Liberati, A Mouraux, J.Delbeke, A.Nonclercq, R. El Tahry.
Effects of acute Transcutaneous Auricular Vagus Nerve Stimulation on EEG oscillations and synchronicity in healthy subjects.
Clinical neurophysiology. IF :4, cited : NA

Abstract
Objectives: Transcutaneous auricular Vagus Nerve Stimulation (taVNS) is proposed as a non-invasive form of VNS. As the latter was shown to induce neural desynchronization, we

investigated how acute taVNS alters brain oscillations and synchrony in healthy subjects.
Methods: We analyzed EEG recordings from 14 healthy subjects, acquired during ± 1h of taVNS (left cymba conchae) and active sham stimulation (left earlobe). We explored time-related effects of: a) the duty cycle, by segmenting each ON and OFF periods into three time windows (T1, T2, T3); b) of the stimulation session, by regrouping EEG epochs into three bins (early, middle and late session time). Using linear mixed models, we compared ON/OFF ratios of whole-brain envelope amplitudes and weighted phase lag index (wPLI) between experimental conditions and factors.
Results: Compared to active sham, we observed a synchronizing effect of taVNS solely in the delta band wPLI (p= 0.034, 'condition' only). No interaction with duty cycle or session time was detected.
Conclusions: taVNS had a synchronizing effect on whole-brain delta rhythms. Yet, we found no specificity of taVNS as compared to active sham when assessing their temporal dynamics.
Significance: taVNS might not alter EEG oscillations with the same mechanisms than invasive VNS.

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- Roberto Santalucia, Evelina Carapancea , Simone vespa, Pascal Vrielynck, Alexane Fierain, Vincent Joris, Christian Raftopoulos, Susana Ferrao Santos, Riëm El Tahry.
Clinical added value of interictal automated electrical source imaging in the presurgical evaluation of MRI-negative epileptic patients: A monocentric prospective study
Epilepsy and Behaviour. IF : 3, cited : NA

Abstract
Objective: During presurgical evaluation, manual electrical source imaging (ESI) provides clinically useful information in one third of the patients but it is time-consuming and requires specific expertise. The aim of this prospective study is to assess the clinical added value of a fully automated ESI analysis in a cohort of patients with MRI-negative epilepsy and describe its diagnostic performance, evaluating sublobar concordance with stereo-electroencephalography (SEEG) results and surgical resection and outcome.
Methods: All consecutive patients referred to the Center for Refractory Epilepsy of St-Luc University Hospital (Brussel, Belgium) for pre-surgical evaluation between 15/01/2019 and 31/12/2020 meeting the inclusion criteria, were recruited to the study. Interictal ESI was realized on low- density long-term EEG monitoring (LD-ESI) and, whenever available, high-density EEG (HD-ESI), using a fully automated analysis (Epilog PreOp, Epilog NV, Ghent, Belgium). The multidisciplinary team (MDT) was asked to formulate hypotheses about epileptogenic zone (EZ) location at sublobar level and make a decision on further management for each patient at two distinct moments: i) blinded to ESI and ii) after presentation and clinical interpretation of ESI. Results leading to a change in clinical management were considered contributive. Patients were followed up to assess whether these changes lead to concordant results on stereo-EEG (SEEG) or successful epilepsy surgery.
Results: Data of all included 29 patients were analyzed. ESI lead to a change in the management plan in 12/29 patients (41%). In 9/12 (75%), modifications were related to a change of the plan of the invasive recording. In 8/9 patients in whom ESI changed the plan of implanting intracranial electrodes, finally underwent invasive recordings. In 6/8 (75%), the intracranial EEG recording confirmed the localization of the ESI at a sublobar level. So far, 5/12 patients, for which management plan was changed after ESI, were operated and have at least one-year

postoperative follow-up. In all cases, the EZ identified by ESI was included in the resection zone. Among these patients, 4/5 (80%) are seizure-free (ILAE 1) and one patient experienced a seizure reduction of more than 50% (ILAE 4).
Conclusions: In this single-center prospective study, we demonstrated the additional value of automated ESI in the presurgical evaluation of MRI-negative cases, especially in helping to plan the implantation of depth electrodes for SEEG, provided that ESI results are integrated in the whole multimodal evaluation and clinically interpreted.
Keywords: Automated ESI, MRI-negative epilepsy, presurgical evaluation

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- Roberto Santalucia, Evelina Carapancea, Simone Vespa, Enrique Germany Morrison, Amir Ghasemi Baroumand, Pascal Vrielynck, Alexane Fierain, Morrison b, Amir Ghasemi Baroumand, Pascal Vrielynck, Alexane Fierain, Vincent Joris, Christian Raftopoulos, Thierry Duprez, Susana Ferrao Santos, Pieter van Mierlo, Riëm El Tahry
Clinical added value of interictal automated electrical source imaging in the presurgical evaluation of MRI-negative epilepsy: A real-life experience in 29 consecutive patients
Epilepsy Behav (IF: 2.94; **Q3**) 2023 Jun;143:109229. doi: 10.1016/j.yebeh.2023.109229.

Abstract
Objective: During the presurgical evaluation, manual electrical source imaging (ESI) provides clinically useful information in one-third of the patients but it is time-consuming and requires specific expertise. This prospective study aims to assess the clinical added value of a fully automated ESI analysis in a cohort of patients with MRI-negative epilepsy and describe its diagnostic performance, by evaluating sublobar concordance with stereo-electroencephalography (SEEG) results and surgical resection and outcome.
Methods: All consecutive patients referred to the Center for Refractory Epilepsy (CRE) of St-Luc University Hospital (Brussels, Belgium) for presurgical evaluation between 15/01/2019 and 31/12/2020 meeting the inclusion criteria, were recruited to the study. Interictal ESI was realized on low-density long-term EEG monitoring (LD-ESI) and, whenever available, high-density EEG (HD-ESI), using a fully automated analysis (Epilog PreOp, Epilog NV, Ghent, Belgium). The multidisciplinary team (MDT) was asked to formulate hypotheses about the epileptogenic zone (EZ) location at sublobar level and make a decision on further management for each patient at two distinct moments: i) blinded to ESI and ii) after the presentation and clinical interpretation of ESI. Results leading to a change in clinical management were considered contributive. Patients were followed up to assess whether these changes lead to concordant results on stereo-EEG (SEEG) or successful epilepsy surgery.
Results: Data from all included 29 patients were analyzed. ESI led to a change in the management plan in 12/29 patients (41%). In 9/12 (75%), modifications were related to a change in the plan of the invasive recording. In 8/9 patients, invasive recording was performed. In 6/8 (75%), the intracranial EEG recording confirmed the localization of the ESI at a sublobar level. So far, 5/12 patients, for whom the management plan was changed after ESI, were operated on and have at least one-year postoperative follow-up. In all cases, the EZ identified by ESI was included in the resection zone. Among these patients, 4/5 (80%) are seizure-free (ILAE 1) and one patient experienced a seizure reduction of more than 50% (ILAE 4).
Conclusions: In this single-center prospective study, we demonstrated the added value of automated ESI in the presurgical evaluation of MRI-negative cases, especially in helping to

plan the implantation of depth electrodes for SEEG, provided that ESI results are integrated into the whole multimodal evaluation and clinically interpreted.
Keywords: Automated ESI; MRI-negative epilepsy; Presurgical evaluation.

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Principal Investigator
Prof. Bernard Hanseeuw, PhD

Postdocs
Lisa Quenon PhD

PhD students
Imaging
Vincent Malotaux
Lise Colmant
Thomas Gérard

Biological analyses (CSF)
Nathalie Nyalu Ngoie

Main collaborators
Adrian Ivanoiu, MD PhD (Neurology)
Renaud Lhommel, MD (Nuclear Medicine)
Laurence Dricot, Ir PhD (Radiology)
Vincent van Pesch, MD PhD (Neurochemistry)
Yves Sznajer, MD (Neurogenetics)
Didier Vertommen, PhD (Mass Spectrometry)

Website
https://uclouvain.be/fr/instituts-recherche/ions/neur/the-louvain-aging-brain-lab.html

Contact
recherche-alzheimer@uclouvain.be
bernard.hanseeuw@uclouvain.be

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- Malotaux V, Dricot L, Quenon L, Lhommel R, Ivanoiu A, Hanseeuw B.
Default-Mode Network Connectivity Changes During the Progression Toward Alzheimer's Dementia: A Longitudinal Functional Magnetic Resonance Imaging Study.
Brain Connectivity. (IF: 2.26; **Q4**)2 023 Jun;13(5):287-296.- doi: 10.1089/brain.2022.0008.

Abstract
Background/Purpose: Brain function changes with Alzheimer's disease (AD) progression. Evaluating those changes longitudinally is important to understand the complex relationships between brain pathologies and cognition. We aimed (1) to identify longitudinal changes in functional connectivity in patients with mild cognitive impairment (MCI) characterized for amyloid- (A) status and (2) to relate these functional changes to clinical progression.
Methods: Forty-four patients with MCI were followed using serial functional magnetic resonance imaging (fMRI) over 1.2 years (three sessions) and cognitive testing over 3.1 years (five sessions). Intra and inter-network connectivities were computed to assess changes in brain connectivity using a network atlas adapted for late adulthood. Sixteen low-A clinically normal older adults underwent a single fMRI session for group comparisons at baseline. Linear mixed-effects models with random intercept and slope were used to predict changes in connectivity based on A status and progression to dementia.
Results: At baseline, intra and inter-network resting-state fMRI connectivities did not differ by baseline clinical diagnosis, A status, or clinical progression to dementia. At the final imaging session, progressive MCI had significantly higher connectivity compared with stable MCI, specifically within the default-mode network (DMN). Longitudinally, progressive MCI had increasing intra-DMN connectivity over time compared with stable MCI, and the rate of changes in connectivity was significantly associated with the rate of cognitive decline.
Conclusions: Intra-DMN connectivity increases in MCI patients progressing toward dementia, suggesting aberrant synchronization in the symptomatic stages of AD.

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- Lebrun L; Hanseeuw B; Van Pesch V ; Ivanoiu A.
Alzheimer disease's cerebrospinal fluid biomarkers differences between immigrants and natives in a Belgian memory clinic.
Acta Neurologica Belgica. (IF: 2.4; **Q4**) 2023 Apr;123(2):537-54 - doi: 10.1007/s13760-022-02143-4

Abstract
Background: Diagnosis of neurodegenerative diseases can raise difficulties among immigrant patients due to language, edu- cational or sociocultural differences with natives. CSF biomarkers of Alzheimer's disease are useful tools to early diagnose neurodegeneration. Yet very few studies have investigated differences of those biomarkers between immigrant and native populations.

Objective: We aimed to characterize differences between CSF biomarkers of Alzheimer's disease within Belgian native and immigrant patients analyzed at Saint Luc Neurochemistry Lab (Brussels, Belgium).
Methods: CSF samples from patients consulting at Saint Luc Memory Clinic (n = 356) or at others hospitals (n = 2430) were analyzed by Saint Luc Neurochemistry Lab between 2010 and 2014. We conducted linear regressions predicting CSF bio- markers with demographic data: age, sex and presumed ethnic origin. For the last one, we subdivided the cohort in natives and immigrants according to their surnames.
Results: Immigrant patients benefit from a CSF sample analysis at a younger age than natives ($p < 0.001$). After linear regressions, age showed a significant impact on all biomarkers ($p < 0.005$). Ethnicity showed a significant impact on T-Tau (p = 0.007) and on T-Tau/amyloid-42 ratio (p = 0.009). Sex showed a significant impact on T-Tau (p = 0.002). ANCOVA analysis suggested that the effect of Age on A_{42} manifests differently according to the ethnicity of the individual.
Conclusion: This study shows higher T-Tau and T-Tau/amyloid-42 ratio values in younger native patients from a Belgian Memory Clinic. A_{42} values tend to follow a different dynamic in time according to the ethnic origin of patients, with patho- logical values at older ages in immigrants.
Keywords Alzheimer's disease · Biomarkers · Cerebrospinal fluid · Ethnicity

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Dr. Emanuel van den Broeke
Postdoctoral researcher, laboratory Algology (prof. André Mouraux),
Institute of Neuroscience (IONS),
Division Systems and Cognition (COSY),
UCLouvain, Brussels
www.nocions.org/emanuel-vandenbroeke

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- Torta DM, Meyers E, Polleunis K, De Wolf S, Meulders A, van den Broeke
The Effect of Observing High or Low Pain on the Development of Central Sensitization.
J Pain. 2023 Jan;24(1):167-177. doi: 10.1016/j.jpain.2022.09.009 -
IF: 5.82; **Q1**). PMID: 36162789 Clinical Trial.

Abstract
It is unknown whether watching other people in high pain increases mechanical hypersensitivity induced by pain. We applied high-frequency electrical stimulation (HFS) on the skin of healthy volunteers to induce pinprick mechanical hypersensitivity. Before HFS participants were randomly allocated to 2 groups: in the low pain group, which was the control condition, they watched a model expressing and reporting lower pain scores, in the high pain group the model expressed and reported higher scores. The 2 videos were selected on the basis of a pilot/observational study that had been conducted before. We tested the differences in perceived intensity of the HFS procedure, in the development of hypersensitivity and the role of fear and empathy. The high pain group reported on average higher pain ratings during HFS. The perceived intensity of hypersensitivity, but not the unpleasantness or the length of the area was higher in the high pain group. Our results suggest that watching a person expressing more pain during HFS increases one's own pain ratings during HFS and may weakly facilitate the development of secondary mechanical hypersensitivity, although this latter result needs replication.
Perspective: Observing a person in high pain can influence the perceived pain intensity of a procedure leading to secondary mechanical hypersensitivity, and has a weak effect on hypersensitivity itself. The role of fear remains to be elucidated.
Keywords: Central sensitization; fear; observational learning; pain.

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

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KU Leuven

Aya Takeoka PhD
Principal Investigator at NERF, a joint research initiative by imec, VIB and KU Leuven
Assistant Professor,
Department of Neuroscience @ KU Leuven
T +32 16 28 31 14
aya.takeoka@nerf.be
www.nerf.be
twitter.com/TakeokaLab

Publication 2022/2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- Bertels H, Vicente-Ortiz G, El Kanbi, K, Takeoka A
  Neurotransmitter phenotype switching by spinal excitatory interneurons regulates locomotor recovery after spinal cord injury
  Nature Neuroscience 25 (5) 617–629. Impact Factor: 24.8

Abstract

Severe spinal cord injury in adults leads to irreversible paralysis below the lesion. However, adult rodents that received a complete thoracic lesion just after birth demonstrate proficient hindlimb locomotion without input from the brain. How the spinal cord achieves such striking plasticity remains unknown. In this study, we found that adult spinal cord injury prompts neurotransmitter switching of spatially defined excitatory interneurons to an inhibitory phenotype, promoting inhibition at synapses contacting motor neurons. In contrast, neonatal spinal cord injury maintains the excitatory phenotype of glutamatergic interneurons and causes synaptic sprouting to facilitate excitation. Furthermore, genetic manipulation to mimic the inhibitory phenotype observed in excitatory interneurons after adult spinal cord injury abrogates autonomous locomotor functionality in neonatally injured mice. In comparison, attenuating this inhibitory phenotype improves locomotor capacity after adult injury. Together, these data demonstrate that neurotransmitter phenotype of defined excitatory interneurons steers locomotor recovery after spinal cord injury.

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Dr. Valerie Uytterhoeven
Staff Scientist Center for Brain & Disease Research,
VIB-KU Leuven Laboratory of neuronal communication
Herestraat 49 bus 602
3000 Leuven
Belgium
Tel: +32 16 37 61 03

Publication 2022/2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- Uytterhoeven, V. et al. (2023)
  Independent pathways contribute to the accumulation of pathogenic Tau at presynapses.
  In preparation:

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Königin-Elisabeth-Stiftung für Medizin
Queen Elisabeth Medical Foundation

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UAntwerpen

Eline Wauters, PhD (VIB)
Neurodegenerative Brain Diseases, VIB Center for Molecular Neurology
Laboratory of Neurogenetics,
Institute Born-Bunge,
University of Antwerp,
Antwerp, Belgium

Publication 2022/2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F.

- Eline Wauters, Helena Gossye, Alexandros Frydas, Anne Sieben and Christine Van Broeckhoven
  Rare exonic variant affects GRN splicing and contributes to frontotemporal degeneration
  Neurobiol Aging (IF: 4.67; **Q2**) . 2023 Jun 16;130:61-69.doi: 10.1016/j.neurobiolaging.2023.06.009.

Abstract

Heterozygous loss-of-function (LOF) mutations in the progranulin gene (*GRN*) cause frontotemporal lobar degeneration (FTLD) by a mechanism of haploinsufficiency. For most missense mutations, the contribution to FTLD is however unclear. We studied the pathogenicity of rare *GRN* missense mutations using patient biomaterials. We identified a new mutation in *GRN*, c.1178 A > C, in a patient with a diagnosis of primary progressive aphasia. Neuropathological examination of autopsied brain showed FTLD with TAR DNA-binding protein 43 (FTLD-TDP) type A pathology with concomitant Alzheimer's disease pathology. Serum pro- granulin protein levels were reduced to levels comparable to known LOF mutations. The mutation is in the last codon of exon 10, in the splice donor sequence. Our data provide evidence that the mutation leads to aberrant splicing, resulting in a frameshift (p.(Glu393AlafsTer31)) and consequently nonsense-mediated mRNA decay. Our finding demonstrates that carefully examining sequencing data around splice sites is needed since this mutation was annotated as a missense mutation. Unraveling the pathogenicity of variants of unknown significance is important for clinical diagnosis and genetic counseling.

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Queen Elisabeth Medical Foundation

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UCB Award 2020

Prof. dr. De Strooper Bart, MD. PhD
VIB Center for Brain and Disease Research
Herestraat 49 3000 Leuven Belgium
E-mail: Bart.Destrooper@vib.be

Publication 2022/2023 with acknowledging G.S.K.E. – F.M.R.E. – Q.E.M.F. – UCB Award

- Disha Shah,Willy Gsell, Je Ro^Me Wahis, Emma S. Luckett, Tarik Jamoulle, Ben Vermaercke, Pranav Preman, Daan Moechars, Ve Ronique Hendrickx, Tom Jaspers, Katleen Craessaerts, Katrien Horre, Leen Wolfs, Mark Fiers, Matthew Holt, Dietmar Rudolf Thal, Zsuzsanna Callaerts-Vegh, Rudi D'hooge, Rik Vandenberghe,
  Uwe Himmelreich, Vincent Bonin, And Bart De Strooper
  Astrocyte calcium dysfunction causes early network hyperactivity in Alzheimer's disease
  Cell Reports 40, 111280, August 23, 2022 - doi: 10.1016/j.celrep.2022.111280.

Summary:
Dysfunctions of network activity and functional connectivity (FC) represent early events in Alzheimer's disease (AD), but the underlying mechanisms remain unclear. Astrocytes regulate local neuronal activity in the healthy brain, but their involvement in early network hyperactivity in AD is unknown. We show increased FC in the human cingulate cortex several years before amyloid deposition. We find the same early cingulate FC disruption and neuronal hyperactivity in AppNL-F mice. Crucially, these network disruptions are accompanied by decreased astrocyte calcium signaling. Recovery of astrocytic calcium activity normalizes neuronal hyperactivity and FC, as well as seizure susceptibility and day/night behavioral disruptions. In conclusion, we show that astrocytes mediate initial features of AD and drive clinically relevant phenotypes.

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

Mailing address:

The scientifique 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

www.fmre-gske.be
www.fmre-gske.eu
www.fmre-gske.com