BRIDGET
BRain Imaging, cognition, Dementia and next generation GEnomics: a Transdisciplinary approach to search for risk and protective factors of neurodegenerative disease

Establishing efficient prevention strategies for dementia and Alzheimer disease (AD) is a major health priority for the coming years. An important hurdle is that pathological processes begin many years before clinical diagnosis, hence efficient prevention should be initiated very early. The BRIDGET Consortium explores the genetic and epigenetic determinants of quantitative MRI-markers of brain aging that are powerful predictors of dementia/AD risk, and examines the clinical significance of the markers in a population-based setting. The outcomes of this project are expected to enrich our understanding of the biological mechanisms underlying early structural brain alterations that portend an increased dementia risk, and thus contribute to the discovery of novel therapeutic targets. The progress of the project since its inception is briefly summarized below (of note, a no-cost extension has been requested and obtained until June 30th 2020).

First, several association analyses of common, low frequency, and rare variants in relation with MRI-markers of brain aging, including previously unexplored ones, have been published or submitted, using elaborate statistical models, in collaboration with additional cohorts from the CHARGE consortium. Phenotypes studied encompass extreme distributions of composite MRI-markers of cerebral small vessel disease; white matter hyperintensity volume; cortical thickness/surface/volume; principal components grouping together cortical regions with shared variance in their surface area; intracranial volume. Additional genetic association analyses at the consortium level are underway, including for novel MRI-markers of brain aging such as dilated perivascular space burden, and composite measures such as the brainage score (manuscripts in preparation). These results are providing important novel insight into common and low frequency variants associated with MRI-markers of brain aging. They also shed new light on changes and genetic determinants of structural brain imaging markers throughout the lifespan.

Second, leveraging JPND and other funds, we have generated two unique resources to study the molecular determinants of MRI-markers of brain aging. One resource consists of a set of ~4,000 middle-aged to older community participants with quantitative brain MRI data and whole genome sequencing. The other resource is a unique set of >1,000 participants with brain MRI data and methyl-C sequencing, selected to represent participants with extreme distributions of cerebral small vessel disease (SVD). By the end of the project this resource will not only provide novel insight into the epigenetic determinants of SVD, but also enable to generate unique high quality reference data for analyses of co-localization for GWAS association signals with blood methylation quantitative trait loci.

Let op; hieronder hangt nog een lange lijst met publicaties!

Manuscripts:

Published

- Duperron MG, Tzourio C, Schilling S, Zhu YC, Soumaré A, Mazoyer B, Debette S**.** *High dilated perivascular space burden: a new MRI marker for risk of intracerebral hemorrhage*. **Neurobiol Aging**. 2019 Sep 10;84:158-165. doi:10.1016/j.neurobiolaging.2019.08.031. [Epub ahead of print] PMID:31629114

- Parker N, Vidal-Pineiro D, French L, Shin J, Adams HHH, Brodaty H, Cox SR, Deary IJ, Fjell AM, Frenzel S, Grabe H, Hosten N, Ikram MA, Jiang J, Knol MJ, Mazoyer B, Mishra A, Sachdev PS, Salum G, Satizabal CL, Schmidt H, Schmidt R, Seshadri S, Schumann G, Völzke H, Walhovd KB, Wen W, Wittfeld K, Yang Q, Debette S, Pausova Z, Paus T. *Corticosteroids and Regional Variations in Thickness of the Human Cerebral Cortex across the Lifespan* **. Cereb Cortex**. 2019 Jun 26. pii: bhz108. doi: 10.1093/cercor/bhz108. [Epub ahead of print]

- Gampawar P, Saba Y, Werner U, Müller-Myhsok B, Schmidt R, Schmidt H. *Evaluation of the performance of AmpliSeq and SureSelect exome sequencing libraries for Ion Proton* **FRONT GENET**. 2019; 10: 856. doi.org/10.3389/fgene.2019.00856

- Janowitz, D, Habes M, Toledo J, Hannemann A, Frenzel S. ,Terock J., Davatzikos C, Hoffmann W, Grabe HJ. *Inflammatory markers and imaging patterns of advanced brain aging in the general population*. **Brain Imaging Behav.** 2019 Mar 1. doi: 10.1007/s11682-019-00058-y. [Epub ahead of print]

- Mishra A, Chauhan G, Violleau MH, Soumare A, Vojinovic D, Jian X, Bis J, Li S, Saba Y, Yang Q, Bartz T, Hofer E, Zhu Y, Mazoyer B, Lathrop M, Schmidt H, Van Duijn C, Ikram MA, Longstreth WT, Fornage M, Seshadri S, Joutel A, Tzourio C, Debette S. *Association of variants in HTRA1 and NOTCH3 with MRI-defined extremes of cerebral small vessel disease in older community persons: an exome sequencing study*. **Brain**. 2019 Apr; 142(4): 1009–1023. Published online 2019 Mar 11. doi: 10.1093/brain/awz024. PMCID: PMC6439324

- Chauhan G, Adams HHH, Satizabal CL, Bis JC, Teumer A, Sargurupremraj M, Hofer E, Trompet S, Hilal S, Smith AV, Jian X, Malik R, Traylor M, Pulit SL, Amouyel P, Mazoyer B, Zhu YC, Kaffashian S, Schilling S, Beecham GW, Montine TJ, Schellenberg GD, Kjartansson O, Guðnason V, Knopman DS, Griswold ME, Windham BG, Gottesman RF, Mosley TH, Schmidt R, Saba Y, Schmidt H, Takeuchi F, Yamaguchi S, Nabika T, Kato N, Rajan KB, Aggarwal NT, De Jager PL, Evans DA, Psaty BM, Rotter JI, Rice K, Lopez OL, Liao J, Chen C, Cheng CY, Wong TY, [...], Ikram MA, Fornage M, Launer LJ, Seshadri S, Longstreth WT Jr, Debette S; Stroke Genetics Network (SiGN),the International Stroke Genetics Consortium (ISGC), METASTROKE, Alzheimer's Disease Genetics Consortium (ADGC), and the Neurology Working Group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium. *Genetic and lifestyle risk factors for MRI-defined brain infarcts in a population-based setting*. **Neurology**. 2019 Jan 16. doi:10.1212/WNL.0000000000006851. [Epub ahead of print]. PMID: 30651383

- Tay N, Macare C, Liu Y, Ruggeri B, Jia T, Chu C, Biondo F, Ing A, Luo Q, Sarkysian D, Banaschewski T, Barker GJ, Bokde ALW, Bromberg U, Büchel C, Quinlan EB, Desrivières S, Flor H, Frouin V, Garavan H, Gowland P, Heinz A, Ittermann B, Martinot JL, Artiges E, Nees F, Orfanos DP, Paus T, Poustka L, Hohmann S, Fröhner JH, Smolka MN, Walter H, Whelan R, Frieling H, Bleich S, Barker ED, Syvänen AC, Rüegg J, Ekström TJ, Bakalkin G, Schumann G; IMAGEN Consortium. *Allele-Specific Methylation of SPDEF: A Novel Moderator of Psychosocial Stress and Substance Abuse*. **Am J Psychiatry** 2019 Feb 1; 176(2):146-155.174(6): 566-575. doi:10.1176/appi.ajp.2018.17121360. Epub 2018 Dec 11. PMID:30525907

- Debette S, Schilling S, Duperron MG, Larsson SC, Markus HS. *Clinical significance of MRI-markers of vascular brain injury. A systematic review and meta-analysis*. **JAMA Neurol**. 2018 Oct 22. doi: 10.1001/jamaneurol.2018.3122.PMID:30422209

- Duperron MG, Tzourio C, Sargurupremraj M, Mazoyer B, Soumaré A, Schilling S, Amouyel P, Chauhan G,Zhu YC, Debette S. *Burden of Dilated Perivascular Spaces, an Emerging Marker of Cerebral SmallVessel Disease, Is Highly Heritable*. **Stroke.** 2018 Feb;49(2):282-287. doi: 10.1161/STROKEAHA.117.019309. Epub 2018 Jan 8.PMID:29311265

- Bourque J, Spechler PA, Potvin S, Whelan R, Banaschewski T, Bokde ALW, Bromberg U, Büchel C, Quinlan EB, Desrivières S, Flor H, Frouin V, Gowland P, Heinz A, Ittermann B, Martinot JL, Paillère-Martinot ML, McEwen SC, Nees F, Orfanos DP, Paus T, Poustka L, Smolka MN, Vetter NC, Walter H, Schumann G, Garavan H, Conrod PJ; IMAGEN Consortium. *Functional Neuroimaging Predictors of Self-Reported Psychotic Symptoms in Adolescents.* **Am J Psychiatry**. 2017 Jun 1;174(6):566-575. doi: 10.1176/appi.ajp.2017.16080897.PMID: 28320226

- O'Halloran L, Cao Z, Ruddy K, Jollans L, Albaugh MD, Aleni A, Potter AS, Vahey N, Banaschewski T, Hohmann S, Bokde ALW, Bromberg U, Büchel C, Quinlan EB, Desrivières S, Flor H, Frouin V, Gowland P, Heinz A, Ittermann B, Nees F, Orfanos DP, Paus T, Smolka MN, Walter H, Schumann G, Garavan H, Kelly C, Whelan R. *Neural circuitry underlying sustained attention in healthy adolescents and in ADHD symptomatology*. **Neuroimage.** 2018 Apr 1;169:395-406. doi: 10.1016/j.neuroimage.2017.12.030. Epub 2017 Dec 21. PMDI : 29274748

- Quinlan EB, Cattrell A, Jia T, Artiges E, Banaschewski T, Barker G, Bokde ALW, Bromberg U, Büchel C, Brühl R, Conrod PJ, Desrivieres S, Flor H, Frouin V, Gallinat J, Garavan H, Gowland P, Heinz A, Martinot JL, Paillère Martinot ML, Nees F, Papadopoulos-Orfanos D, Paus T, Poustka L, Smolka MN, Vetter NC, Walter H, Whelan R, Glennon JC, Buitelaar JK, Happé F, Loth E, Barker ED, Schumann G; IMAGEN Consortium. *Psychosocial Stress and Brain Function in Adolescent Psychopathology.* **Am J Psychiatry**. 2017 Aug 1;174(8):785-794. doi: 10.1176/appi.ajp.2017.16040464. Epub 2017 Jun 16. PMID:28618856

- Sadaghiani S, Ng B, Altmann A, Poline JB, Banaschewski T, Bokde ALW, Bromberg U, Büchel C, Burke Quinlan E, Conrod P, Desrivières S, Flor H, Frouin V, Garavan H, Gowland P, Gallinat J, Heinz A, Ittermann B, Martinot JL, Paillère Martinot ML, Lemaitre H, Nees F, Papadopoulos Orfanos D, Paus T, Poustka L, Millenet , Fröhner JH, Smolka MN, Walter H, Whelan R, Schumann G, Napolioni V, Greicius M (2017). *Overdominant Effect of a CHRNA4 Polymorphism on Cingulo-Opercular Network Activity and Cognitive Control*. **J Neurosci**. 2017 Oct 4;37(40):9657-9666. doi: 10.1523/JNEUROSCI.0991-17.2017. Epub 2017 Sep 6. PMID: 28877969.

- Malik R, Chauhan G, Traylor M, Sargurupremraj M, Okada Y, Mishra A, Rutten-Jacobs L, Giese AK, van der Laan SW, Gretarsdottir S, Anderson CD, Chong M, Adams HHH, […], Teumer A, Tomppo L, Torres-Aguila NP, Touze E, Tsugane S, Uitterlinden AG, Valdimarsson EM, van der Lee SJ, Völzke H, Wakai K, Weir D, Williams SR, Wolfe CDA, Wong Q, Xu H, Yamaji T, Sanghera DK, Melander O, Jern C, Strbian D, Fernandez-Cadenas I, Longstreth WT Jr, Rolfs A, Hata J, Woo D, Rosand J, Pare G, Hopewell JC, Saleheen D, Stefansson K, Worrall BB, Kittner SJ, Seshadri S, Fornage M, Markus HS, Howson JMM, Kamatani Y, Debette S*, Dichgans M* *co-corresponding authors . *Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes*. **Nat Genet**. 2018 Apr;50(4):524-537. doi: 10.1038/s41588-018-0058-3. Epub 2018 Mar 12. PMID:2953135

Submitted / Under review / In revision

- Hofer E , Roshchupkin G , Adams HHH , Knol M , Lin H, Li S, Zare H , Ahmad S, Armstrong N, Satizabal C , Bernard M , Bis J , Gillespie N, Luciano M, Mishra A, Scholz M, Teumer A, Xia R, Jian X, Mosley T, Saba Y, Pirpamer L , Seiler S, Becker J, Carmichael O, Rotter J, Psaty B, Lopez O, Amin N , van der Lee S, Yang Q, Himali J, Maillard P, Beiser A, DeCarli C, Karama S, Lewis L, Bastin M, Deary I, Witte AV, Beyer R, Loeffler M, Mather K, Schofield P, Thalamuthu A, Kwok J, Wright M, Ames D, Trollor J, Jiang J, Brodaty H, Wen W, Vernooij M, Hofman A, Uitterlinden A, Niessen W, Wittfeld K, Bülow R, Völker U, Pausova Z, Pike GB , Maingault S, Crivello F, Mazoyer M, Neale M, Franz C, Lyons M, Panizzon M, Andreassen O, Dale A, Logue M, Grasby K, Jahanshad N, Painter J, Colodro Conde L, Bralten J, Hibar D, Lind P, Pizzagalli F, Stein J, Thompson P, Medland S, Sachdev P, Kremen W, Wardlaw J, Villringer A, van Duijn C, Grabe H, Longstreth W, Fornage M, the SYS , Debette S, Ikram MA, Schmidt H, Schmidt R, Seshadri S. *Genome-wide association study (GWAS) of cortical thickness, surface area and volume*. 2019, in revision
- Grasby et al. *The genetic architecture of the human cerebral cortex*. 2019, in revision

- Sargurupremraj M, Suzuki H, Jian X, Sarnowski C, Evans TE, [..], Tzourio C, Adams HH, Matthews PM, Fornage M, Debette S. *Cerebral small vessel disease genomics: implications across the life span*. 2019, under review
- Shin J, Ma S, Hofer E, Patel Y, Roshchupkin GV, Sousa AM, Jian9 X, Gottesman RF , Mosley TH, Fornage M, Saba Y, Pirpamer L, Schmidt R, Schmidt H, Mazoyer B, Carrion-Castillo A, Bis JC, Li S, Yang Q, Luciano M, Karama S, Lewis L, Bastin ME, Harris MA, Deary IJ, Wardlaw JM, Scholz M, Loeffler M, Witte V, Beyer F, Villringer A, Adams HHH, Ikram MA, Kremen WS, Gillespie NA, the ENIGMA Consortium, Sestan3 N, Pausova Z, Seshadri S, Paus T; for the neuroCHARGE Working Group. *Planar cell polarity pathway and development of the human visual cortex.* 2019, submitted

<u>In Preparation - currently being finalized for submission</u>

- M Knol et a. *Intracranial volume GWAS meta-analysis*
- MG Duperron et al. *Dilated perivascular space burden*
- Y Saba et al. *Genetics of white matter hyperintensity stratified on hypertension status.*
- G Beaudet et al. *Diffusion tensor imaging markers of brain aging across the lifespan*.
- S Frenzel et al. *Genetics of the Brain age score*