CCNA/CCNV Team 9 Bulletin

Biomarkers of Aging and Neurodegeneration
Co-Leads: Roger A. Dixon and M. Natasha Rajah
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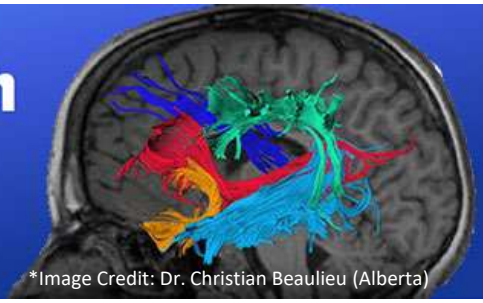

*Image Credit: Dr. Christian Beaulieu (Alberta)

Greetings from CCNA/CCNV Team 9

This newsletter is a periodic publication from Team 9 of the Canadian Consortium on Neurodegeneration in Aging (CCNA). Since its inception in the earliest days of CCNA, the team Co-Leads have been **Roger A. Dixon** (Alberta) and **Pierre Bellec** (Montréal). In 2022, after much deliberation, Pierre decided to step down from his Co-Lead role. Although we will miss Pierre's important contributions to various team administrative and planning initiatives, we are pleased that he will continue with his many team-related collaborative research and training activities. Many thanks to Pierre for his excellent contributions to Team 9! We are delighted to announce that **M. Natasha Rajah** (McGill) has agreed to become the next Team 9 Co-Lead. *For an introduction to Natasha, please see page 2 of this newsletter*. Roger and Natasha will manage the team according to the mandate from our main funding partners by continuing to develop and apply a variety of "neuroinformatics" approaches (including AI, omics, machine learning, big data, precision subtypes) to address the heterogeneous, interactive and dynamic nature of the continuum from healthy brain aging to dementia. The team will adhere to our four original goals: (1) Coordinate biomarker discovery and validation with multiple approaches; (2) Integrate core biomarker development in multiple modalities with risk and resilience factors; (3) Initiate new synergistic and leveraging collaborations within and across CCNA teams, platforms, and programs; and (4) Promote training, visibility, productivity, and participation in CCNA.

Salutations de l'équipe CCNV/CCNA 9

Ce bulletin est une publication périodique issu de l'équipe 9 du Consortium canadien sur la neurodégénérescence associée au vieillissement (CCNV). Depuis sa création, les co-dirigeants de l'équipe ont été **Roger A. Dixon** (Alberta) et **Pierre Bellec** (Montréal). En 2022, après une longue réflexion, Pierre a décidé de se retirer de son rôle de co-dirigeant. Bien que les contributions importantes de Pierre aux diverses initiatives d'administration et de planification de l'équipe nous manqueront, nous sommes heureux qu'il va continuer à poursuive ses activités de recherche et de collaboration avec notre équipe. Un grand merci à Pierre pour ses excellentes contributions à l'équipe 9! Nous sommes ravis d'annoncer que **M. Natasha Rajah** (McGill) a accepté de devenir la prochaine co-dirigeante de l'équipe 9. *Pour obtenir plus d'information sur le parcours de Natasha, veuillez consulter la page 2 de ce bulletin*. Roger et Natasha dirigeront l'équipe conformément au mandat de nos partenaires de financement en continuant à développer et à appliquer une variété d'approches « neuroinformatiques » (y compris l'intelligence artificielle, les multi-omiques, l'apprentissage automatique, les mégadonnées, les sous-types de précision) pour aborder un continuum hétérogène et dynamique allant du vieillissement sain à la démence. L'équipe adhèrera à nos quatre objectifs initiaux: (1) Coordonner la découverte et la validation de biomarqueurs via plusieurs approches; (2) Intégrer le développement de biomarqueurs dans de multiples modalités avec des facteurs de risque et de résilience; (3) Initier de nouvelles collaborations synergiques à travers les équipes, platesformes et programmes du CCNV; et (4) Promouvoir la formation, la visibilité, la productivité et la participation au CCNV.

CCNA Canadian Consortium on Neurodegeneration in Aging | CCNV Consortium canadien en neurodégénérescence associée au vieillissement | ALBERTA INNOVATES | CCNA T9 NiNet Neuroinformatics Network | CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

Dr. M. Natasha Rajah: New CCNA Team 9 Co-Lead

We are pleased to announce that Dr. M. Natasha Rajah has been appointed as the new Co-Lead of CCNA Team 9. Natasha received her Ph.D. in Psychology (with an emphasis on neuroimaging) from the University of Toronto and did her post-doctoral training at the Helen Wills Neuroscience Institute, University of California at Berkeley. She joined McGill University and the Douglas Research Centre as an Assistant Professor in 2005. She is currently Full Professor and Assistant Dean (Academic Affairs) at Faculty of Medicine and Health Sciences, McGill. She holds a CIHR Sex and Gender Research Chair in Neuroscience, Mental Health, and Addiction and has served as Chair of the Membership Committee and Co-Chair of the EDI committee at CCNA. She is also a member of the Institute Advisory Board for the Institute of Aging at CIHR and on the Board of Directors, Canadian Association of Neuroscience.

Dr. Rajah's innovative cognitive neuroscience research program studies diverse individuals, with varied levels of Alzheimer's disease risk factors, to understand how biological sex, gender, and social determinants of health (SDH) and lifestyle factors interact with and affect memory and brain health across the adult lifespan. Her past work has helped quantify the large-scale neural networks that support successful episodic memory function in adults; highlighted that age does not affect all episodic memory processes equally; and shown that middle-age is a critical, yet understudied, period in adulthood when episodic memory declines and genetic risk factors for late-onset AD (i.e., +APOE4 status) begin to affect memory-related brain function. Her recent cognitive neuroscience of aging research has examined how biological sex and individual differences in SDH and lifestyle factors contribute to brain health and memory function in middle-aged and older females and males.

Selected Recent References

Subramaniapillai, S. et al. ***Age- and episodic memory-related differences in task-based functional connectivity in women and men***. *J Cogn Neurosci* **34**, 1500-1520 (2022). https://doi.org/10.1162/jocn_a_01868

Snytte, J. et al. ***Volume of the posterior hippocampus mediates age-related differences in spatial context memory and is correlated with increased activity in lateral frontal, parietal and occipital regions in healthy aging***. *Neuroimage* **254**, 119164 (2022). https://doi.org/10.1016/j.neuroimage.2022.119164

Subramaniapillai, S. et al. ***Sex and gender differences in cognitive and brain reserve: Implications for Alzheimer's disease in women***. *Front Neuroendocrinol* **60**, 100879 (2021). https://doi.org/10.1016/j.yfrne.2020.100879

Rabipour, S. et al. ***Generalization of memory-related brain function in asymptomatic older women with a family history of late onset Alzheimer's disease: Results from the PREVENT-AD Cohort***. *Neurobiol Aging* **104**, 42-56 (2021). https://doi.org/10.1016/j.neurobiolaging.2021.03.009

Wang, H. et al. ***Sex differences in the relationship between age, performance, and BOLD signal variability during spatial context memory processing***. *Neurobiol Aging* **118**, 77-87 (2022). https://doi.org/10.1016/j.neurobiolaging.2022.06.006

Corriveau-Lecavalier, N. et al. ***Sex differences in patterns of associative memory-related activation in individuals at risk of Alzheimer's disease***. *Neurobiol Aging* **119**, 89-101 (2022). https://doi.org/10.1016/j.neurobiolaging.2022.07.007

Elshiekh, A. et al. ***The association between cognitive reserve and performance-related brain activity during episodic encoding and retrieval across the adult lifespan***. *Cortex* **129**, 296-313 (2020). https://doi.org/10.1016/j.cortex.2020.05.003

Cabeza, R. et al. ***Maintenance, reserve, and compensation: The cognitive neuroscience of healthy ageing***. *Nature Reviews: Neuroscience* **19**, 701-710 (2018). https://doi.org/10.1038/s41583-018-0068-2

Rajah, M.N. et al. ***Family history and APOE4 risk for Alzheimer's disease impact the neural correlates of episodic memory by early midlife***. *Neuroimage Clin* **14**, 760-774 (2017). https://doi.org/10.1016/j.nicl.2017.03.016

CCNA Team 9 Participates in 2022 Science Days

Team 9 members and trainees were quite active in the 2022 CCNA Science Days program. The team contributions included invited addresses, poster presentations, and moderating roles. Here is a list of known Team 9 contributions.

Invited Addresses

Keynote Address: Alan Evans (McGill University), ***Pathology progression modelling in Alzheimer's disease***. Moderator: Simon Duchesne (Laval University)

Keynote Address: Michelle M. Mielke (Wake Forest University), ***What about SeXX? Importance of considering sex and gender in Alzheimer's and aging research***. Moderators: Roger A. Dixon (University of Alberta) and Rebekah Reuben (University of Toronto)

Invited Address: G. Peggy McFall (University of Alberta), ***Methodological approaches to integrating sex and gender analyses in large-scale databases of aging and Alzheimer's disease***.

Poster Presentations (Trainee names underlined)

CONFERENCE TRAINEE AWARD (Post-Doctoral Category):** Bohn, L., Drouin, S.M., McFall, G.P., Rolfson, D., Andrew, M.K., & Dixon, R.A. (2022, October). ***Machine learning analyses identify multimorbidity features that discriminate four cohorts in the Alzheimer's disease spectrum: A COMPASS-ND study.

Caballero, H.S., McFall, G.P., Heal, M., Vergote, D., Andrews, S.J., Jhamandas, J.H., Westaway, D., Masellis, M., & Dixon, R.A. (2022, October). ***Do polygenic risk scores representing Alzheimer's global risk or specific mechanisms predict non-demented memory aging trajectories differently in females and males?***

Drouin, S.M., Badhwar, A., McFall, G.P., Bohn, L., Sapkota, S., Lussier, D., Descoteaux, M., Black, S., Chertkow, H., Rajah, M.N., Masellis, M., Greiner, R., Li, L., Iturria-Medina, Y., Duchesne, S., Dixon, R.A. (2022, October). ***Integrating neuroinformatics and multiomics biomarker approaches to understanding heterogeneity and precision in Alzheimer's and related dementias: A COMPASS-ND protocol from CCNA Team 9***.

Heal, M., McFall, G.P., Caballero, H.S., Vergote, D., Westaway, D., Jhamandas, J.H., & Dixon, R.A. (2022, October). ***Integrating Alzheimer's genetic risk, vascular health, and sex in predicting memory aging trajectories: Two replicated multi-step biomarker network analyses***.

CONFERENCE TRAINEE AWARD (Master's Student Category):** Helbling, C., & DeMarco, M.L. (2022, October). ***Diagnostic performance of α-synuclein seeding amplification assays using cerebrospinal fluid, skin, and olfactory mucosa: A meta-analysis.

CONFERENCE TRAINEE AWARD (Doctoral Student Category):** Khushbu, J.P., Yang, D., Feldman, H.H., Hsiung, G.-Y., Nygaard, H.B., Best, J.R., Dwosh, E., Robillard, J.M., & DeMarco, M.L. (2022, October). ***The importance of early diagnosis: Lessons learned from lived experiences in the IMPACT-AD BC study.

Lussier, D., Clarke, N., Wang, H.-T., Boré, A., Tetrel, L., Devenyi, G.A., Beaulieu, C., Chakravarty, M.M., Descoteaux, M., Dixon, R.A., Duchesne, S., Badhwar, A., & Bellec, P. (2022, October). ***Preprocessed neuroimaging derivatives for the Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) Study***.

McFall, G.P., Bohn, L., Gee, M., Drouin, S.M., Han, W., Li, L., Camicioli, R., & Dixon, R.A. (2022, October). ***Identifying key multi-modal predictors of incipient dementia in Parkinson's disease: A machine learning analysis and Tree SHAP interpretation*.**

****Note: Award Winning Trainee Presentations are described elsewhere in this newsletter.***

Highlights from the Mari L. DeMarco Lab at the 2022 CCNA Science Days

Dr. Mari DeMarco is a member of Team 9 and Principal Investigator of the impressively productive IMPACT-AD Project at the University of British Columbia. At the recent CCNA Partners Forum and Science Days (October 2022), two trainees in Dr. DeMarco's group received awards for their outstanding poster presentations. **Khushbu Patel** and **Cyril Helbling** were awarded best CCNA Theme 2 (Diagnosis and Treatment) posters in separate student categories.

Khushbu Patel's work, titled *The importance of early diagnosis: Lessons learned from lived experiences in the IMPACT-AD BC study,* was awarded Best Poster in the Master's category. (The co-authors were: Yang, D, Feldman, HH, Hsiung, GY, Nygaard, HB, Best, JR, Dwosh, E, Robillard, JM, & DeMarco, ML.) Khushbu completed three years of clinical work at the University of Nairobi Medical School in Kenya before obtaining a Bachelor's of Science from Trent University in Ontario. She is currently completing her Master's degree, working with individuals living with neurodegenerative diseases, and their family and friends, to bring their voices to the forefront of decisions surrounding Alzheimer's disease biomarker testing.

Cyril Helbling presented on the *Diagnostic performance of α-synuclein seeding amplification assays using cerebrospinal fluid, skin, and olfactory mucosa: A meta-analysis*. He was awarded Best Poster in the Doctoral, MD/PhD category. (The co-authors were: Heibling, C, Yeung, S, & DeMarco, ML.) Cyril obtained his Bachelor's and Master's degrees in Chemistry with a specialization in biochemistry and analytical chemistry at the Swiss Federal Institute of Technology in Lausanne, Switzerland. Cyril started his UBC PhD program in the fall of 2022 in the DeMarco Lab and is developing a biomarker tool for the detection of synucleinopathies including Parkinson's disease and Lewy body dementia.

For more information about Dr. DeMarco and her IMPACT-AD project please see:
Alzheimer's disease | IMPACT AD | Canada

Update on Team 9 Neuroinformatics in Neurodegeneration Network

This Team 9 network is designed to conduct multi-disciplinary research on aging and neurodegenerative diseases that accommodate and evaluate a broad spectrum of biomarker domains and approaches. Our first Team 9 signature article was led by then-trainees, Drs. AmanPreet Badhwar, G. Peggy McFall, and Shraddha Sapkota. It provided a "roadmap" from multi-omics (connectomics, metabolomics, genomics) through machine learning analytics to subtypes of heterogeneous neurodegenerative diseases, such as Alzheimer's.

Badhwar, A., McFall, G.P., Sapkota, S., Black, S., Chertkow, H., Duchesne, S., Masellis, M., Li, L., Dixon, R.A., & Bellec, P. (2020). ***A multiomics approach to heterogeneity in Alzheimer's disease: Focused review and roadmap***. *Brain*, 143(5), 1315-1331. https://doi.org/10.1093/brain/awz384

Our follow-up Team 9 article is in preparation. This paper is designed to provide a neuroinformatics protocol (incorporating artificial intelligence and related technologies) for analyzing and interpreting multi-modal data from the CCNA COMPASS-ND database. The first version was presented at the 2022 CCNA Science Days.

Drouin, S.M., Badhwar, A., McFall, G.P., Bohn, L., Sapkota, S., Lussier, D., Descoteaux, M., Black, S., Chertkow, H., Rajah, M.N., Masellis, M., Greiner, R., Li, L., Iturria-Medina, Y., Duchesne, S., Dixon, R.A. (2022, October). ***Integrating neuroinformatics and multiomics biomarker approaches to understanding heterogeneity and precision in Alzheimer's and related dementias: A COMPASS-ND protocol from CCNA Team 9***. Presented at the 2022 Virtual CCNA Science Days Conference.

Dr. Linzy Bohn: CCNA Science Days 2022

Dr. Linzy Bohn's poster was selected as an award recipient in the Postdoctoral category at the 2022 CCNA Partners Forum and Science Days. Dr. Bohn is a PDF working under the supervision of Dr. Roger Dixon at the University of Alberta. Her research program centers on the application of data-driven analytic techniques (e.g., machine learning) to large-scale longitudinal studies of aging, biomarkers, and neurodegenerative disease. The overarching aims are to advance research integrating and comparing large sets of factors from multiple modalities, including Alzheimer's biomarkers (e.g., genetic, molecular), frailty morbidities (e.g., biomedical), risk factors (e.g., lifestyle), and demographics (e.g., sex) in the precision prediction of differential aging trajectories and clinical outcomes (e.g., dementia). She specializes in both large-scale longitudinal and multiple cohort data analytics (e.g., COMPASS-ND).

Bohn, L., Drouin, S.M., McFall, G.P., Rolfson, D., Andrew, M.K., & Dixon, R.A. (2022, October). ***Machine learning analyses identify multimorbidity features that discriminate four cohorts in the Alzheimer's disease spectrum: A COMPASS-ND study***. Presented at the 2022 Virtual CCNA Science Days Conference.

Dr. Jodie Gawryluk: New Team 9 Member

Jodie Gawryluk, PhD, R.Psych., is a Clinical Neuropsychologist and Associate Professor in the Department of Psychology, cross-appointed in the Division of Medical Sciences, at the University of Victoria. Her research combines neuropsychology and magnetic resonance imaging (MRI) techniques, including diffusion tensor imaging and functional MRI, to study the brain-behavior relationship in healthy aging and in neurodegenerative disorders. She has used multimodal imaging approaches to investigate longitudinal changes in structural and functional connectivity in older adults and how variability in the fMRI signal relates to aging. Her group is particularly interested in using MRI methods to detect changes in the brain before changes in cognition are measurable. Consequently, they have focused on individuals with subjective cognitive decline (SCD), who may be at risk for developing dementia. Interestingly, they detected differences between the SCD and healthy control cohorts in white matter integrity and functional connectivity, but not grey matter atrophy.

Parker, A.F., Smart, C.M., Scarapicchia, V., Gawryluk, J.R., for the Alzheimer's Disease Neuroimaging Initiative. ***Identification of earlier biomarkers for Alzheimer's disease: A multimodal neuroimaging study of individuals with subjective cognitive decline***. J Alzheimer's Dis. 2020; 77(3):1067-1076. https://doi.org/10.3233/JAD-200299

Team 9 Members: Roger A. **Dixon** (Alberta), M Natasha **Rajah** (McGill), AmanPreet **Badhwar** (Montréal), Robert **Bartha** (Western), Christian **Beaulieu** (Alberta), Pierre **Bellec** (Montréal), Sandra **Black** (Sunnybrook), Richard **Camicioli** (Alberta), Mallar **Chakravarty** (McGill), Ting-Huei **Chen** (Laval), Howard **Chertkow** (Sunnybrook), D. Louis **Collins** (McGill), Mahsa **Dadar** (McGill), Mari **DeMarco** (UBC), Maxime **Descoteaux** (Sherbrooke), Simon **Duchesne** (Laval), Alan **Evans** (McGill), Esther **Fujiwara** (Alberta), Jodie **Gawryluk** (Victoria), Scott **Hofer** (Victoria), Zahinoor **Ismail** (Calgary), Yasser **Iturria-Medina** (McGill), Liang **Li** (Alberta), Nikolai **Malykhin** (Alberta), Josefina **Maranzano** (Québec à Trois-Rivières), Mario **Masellis** (Sunnybrook), Joanne A. **Matsubara** (UBC), G. Peggy **McFall** (Alberta), Sridar **Narayanan** (McGill), Jacqueline **Pettersen** (UNBC), Marc J. **Poulin** (Calgary), Hyman **Schipper** (McGill), Eric **Smith** (Calgary), Peter **Stys** (Calgary), Sylvia **Villeneuve** (McGill), David **Westaway** (Alberta), David **Wishart** (Alberta).

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