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IC-P-141: Exercise to enhance hippocampal function and memory in older adults: Proof of concept findings from a 12-week exercise intervention trial

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ADNI dataset. 17 features served as inputs to the classifier: three MRI intensities (T1-w, T2*, and FLAIR), spatial probability map, intensity distribution probabilities for healthy and WMH tissues (P_{WM}/P_{WMH}) as well as the ratio P_{WM}/P_{WMH} for each modality, and the average intensity of healthy tissue at each voxel for each modality. WMHs were segmented using a linear regression classifier with thresholding yielding low variance, high accuracy and low computation time. Performance was evaluated with 10-fold cross-validation, using Dice Kappa similarity, sensitivity, and specificity to compare automated and manual labels. **Results:** The mean Dice Kappa, sensitivity, and specificity between automated and manual labels were 0.46, 0.55, and 0.999, respectively. For further validation, total WMH loads were correlated with Fazekas scores of 30 subjects ($r=0.80$, $p=6.44e-7$ for periventricular and $r=0.55$, $p=2.8e-3$ for deep WMHs) as well as age for the total population ($r=0.43$, $p=1.52e-6$). Figures 1.a., 1.b. and 1.c. show the FLAIR images, and automated and manual labels for a subject. Figures 1.d. and 1.e. show Kappa and sensitivity/specificity versus threshold. **Conclusions:** Automated labels showed reasonable agreement with manual labels and had significant correlations with Fazekas ratings. Our results therefore suggest that the proposed automated tool can provide fast, robust, and accurate labels for WMHs and holds good potential for clinical studies. (Funding: CIHR MOP-111169, Pfizer Canada, FRQ-S, and Douglas Hospital Research Centre)

IC-P-140 ASSOCIATIONS BETWEEN YEARS OF EDUCATION, A β DEPOSITION, AND METABOLISM IN COGNITIVELY NORMAL OLDER ADULTS, MILD COGNITIVE IMPAIRMENT, AND ALZHEIMER'S DISEASE: EVIDENCE FOR RESERVE

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Background: Cognitive reserve (CR) may provide resilience against amyloid- β (A β) pathology and thus delay clinical symptoms of Alzheimer's disease (AD). However, neurophysiological mechanisms underlying CR are poorly understood. Furthermore, relationships between surrogates of CR and A β may differ across the cognitive spectrum: some evidence suggest that surrogates of CR are related to lower A β pathology in cognitively normal older adults, while the reverse has been found in AD patients. Therefore, we first assessed relationships between years of education (a surrogate of CR) and A β deposition in normal older adults, mild cognitive impairment (MCI) and AD. Second, we studied potential neurophysiological mechanisms underlying CR using a multimodal neuroimaging approach. **Methods:** Fifty-six normal older adults, 29 MCI and 21 AD patients underwent florbetapir-PET, FDG-PET and MRI examinations. In a first step, voxel-wise correlations between years of education and florbetapir-PET were assessed within each group, including age, sex and global cognitive function as nuisance variables. Further multimodal analyses (i.e., with gray matter volume and glucose metabolism) were

carried out within the group where relationships between A β and years of education were significant ($p<0.05$ FDR corrected). **Results:** Higher years of education were related to increase A β deposition in frontal, parietal and temporal regions in MCI patients ($r=0.6$, $p=0.002$; Figure 1A). Such association was not found in normal older adults and AD when assessed voxel-wise, but it was recovered in AD when specifically assessing the same brain areas ($r=0.42$, $p=0.05$; Figure 1A). Complementary analyses in MCI revealed i) increased metabolism related to higher years of education within these areas (Figure 1B) and ii) a positive relationship between education-related A β increases and education-related increases in metabolism ($r=0.6$, $p=0.001$; Figure 1C). **Conclusions:** Our results may have different implications; first, considering normal older adults, MCI and AD, education-related compensation for A β appears to be maximal at MCI stage. Second, higher metabolism in higher educated MCI patients may protect against the deleterious effects of A β deposition such that more A β deposition would be needed in higher educated MCI patients to convert to AD. Overall, we provide new insights into how CR may delay A β effects on cognition.

IC-P-141 EXERCISE TO ENHANCE HIPPOCAMPAL FUNCTION AND MEMORY IN OLDER ADULTS: PROOF OF CONCEPT FINDINGS FROM A 12-WEEK EXERCISE INTERVENTION TRIAL

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Background: Exercise has emerged as a promising lifestyle intervention to help remediate cognitive loss or delay onset of dementia. To fully capitalize on the investments made in exercise and to discover the full treatment potential of exercise, understanding brain mechanisms that support cognitive benefits in older adults must be understood. The objective of this pilot study was to test the feasibility of an exercise intervention to

improve hippocampal-dependent memory processing for pattern separation and completion. We assessed recruitment, retention, adherence, data collection using fMRI and pre-post brain imaging analysis in a community-based sample of older adults. **Methods:** We conducted a phase II proof of concept, treatment arm only study to assess feasibility of collecting novel neuroimaging and cognitive outcome measures in an exercise trial. The 12-week exercise program included a 60-minute, twice a week, moderate-intensity, group program led by a fitness instructor at a local senior center. Primary outcomes were a memory recognition index and associated levels of fMRI hippocampal activity. Secondary outcomes for physical function were also measured. **Results:** We screened 53 individuals and recruited 10 inactive, community-dwelling, non-demented older adults with typical cognition or mild cognitive impairment (mean age: 67±5 years, 60% women). Retention was 90%, as one participant withdrew in week 3. Adherence was 85%, as measured by class attendance. 30% fit criteria for early MCI, 38% were APOE-ε4 carriers, and 50% were BDNF Val66Met carriers. Pre-post comparisons suggest an effect size of 0.57 for the memory recognition index and 2.3 for fMRI hippocampal activity. Effect sizes for physical function measures were 2.4 for chair stand, 0.94 for timed up-and-go, and 0.48 for functional reach. **Conclusions:** Conducting an exercise intervention study that measures memory function and hippocampal activity using fMRI is feasible in older adults, including in individuals with MCI. A randomized controlled trial of exercise is warranted and may supply evidence of the treatment target / engagement and therapeutic changes in brain mechanisms associated with increased exercise in older adults at risk for Alzheimer's disease.

Figure 1. Hypothesized pathway of target engagement in exercise.

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EFFECT OF MODERATE-HIGH INTENSITY AEROBIC EXERCISE ON BETA-AMYLOID ACCUMULATION MEASURED WITH ¹¹C-PIB-PET IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE

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Background: Physical exercise may be an adjunct to treatment of Alzheimer's disease (AD). Several studies have indicated a beneficial effect of physical activity on symptoms of AD, but biological mechanisms underlying this effect remains relatively uninvestigated.

The objective of the present study was to investigate whether moderate-high intensity aerobic exercise reduces the accumulation of beta-amyloid in AD. **Methods:** The ADEX study is a multi-center randomized, controlled trial, which aimed to investigate the impact of a supervised aerobic exercise program on symptoms and biomarkers of AD. Two hundred patients with mild AD were randomized to either an exercise group (60-minute exercise sessions three times a week for 16 weeks) or to a control group. A subgroup underwent ¹¹C-PIB-PET and 3-Tesla MRI for quantification of beta-amyloid deposition. The PET standardized uptake values (SUV) were measured 40-70 min post injection from segmented cortical regions of interest using PVE-lab. Data were normalized to gray matter cerebellum SUV resulting in a region-to-cerebellar ratio (SUVR). Between-group difference in change in global SUVR (lateral temporal cortex, posterior cingulate, anterior cingulate, precuneus, parietal cortex, and lateral prefrontal cortex) from baseline was assessed using un-paired t-test. **Results:** Thirtyfour participants (mean; ± SD] Age: 68.9; ±7.9, baseline MMSE: 25.6; ±2.7, gender [f/m]: 16/18) underwent MRI and ¹¹C-PIB-PET at baseline. At baseline 15 subjects were randomized to the intervention, 19 to the control group. There was no significant difference between groups in baseline variables (age, gender, MMSE). Baseline SUVR was for the intervention group 2.32 (1.18-2.79), and control group 2.04 (1.15-2.65). There was an increase in SUVR from baseline to follow-up (intervention group: 0.040; ±0.033 vs. control group: 0.025; ±0.029) in both groups but no significant between-group difference in change from baseline between the intervention and control group (p=0.74). **Conclusions:** The present findings do not support an effect of physical exercise on global beta-amyloid deposition in patients with AD. Longer duration of interventions, either of each exercise schedule or trial period, as well as higher intensity of exercise, may be needed in order to affect global beta-amyloid deposition.

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FEASIBILITY OF A COGNITIVE REHABILITATION GROUP PROGRAM FOR PATIENTS WITH MILD DEMENTIA IN ALZHEIMER'S DISEASE: A RANDOMIZED, CONTROLLED, SINGLE-BLINDED PILOT STUDY

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Background: Recent studies suggest that cognitive rehabilitation in the treatment of Alzheimer's disease (AD) enhances the patients' ability to mobilise personal resources to compensate the loss of cognitive functioning. Cognitive rehabilitation aims at the maintenance of autonomy and quality of life. We investigated the feasibility and effectiveness of a multimodal individualized group rehabilitation program for people with mild AD dementia. **Methods:** We adapted an individualised manual-guided cognitive rehabilitation program (CORDIAL, Werheid et al. 2010) to a group-setting. To allow a standardised repeatability and comparison, we chose the manual-based approach. Additionally, we implemented a group-setting, to support the patients' social interaction and sense of coherence, but also to provide a potentially cost-efficient, feasible treatment. Individual strategies pursue the independent performance of meaningful activities; integrating the care-giver enhances a sustainable transfer into everyday-life. To enhance compensating resources, we offer relaxation-therapy and