Study Protocol

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Words on the Brain: Can Reading Rehabilitation for Age-Related Vision Impairment Improve Cognitive Functioning?

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Age-related vision impairment and cognitive impairment both become more prevalent with increasing age. Research into their mechanisms has suggested that for some of these conditions (e.g., macular degeneration/glaucoma and Alzheimer's disease) there may be an underlying common cause, or they may be causally linked to a multifactorial context of frailty. Furthermore, a pressing goal of sensory-cognitive aging research is to investigate the possibility that age-related sensory deprivation may accelerate the progression of cognitive decline. For example, hearing loss in mid-life has been identified as the strongest potentially modifiable risk factor for cognitive impairment in later life. Research has demonstrated that hearing rehabilitation may have a beneficial effect on cognitive functioning insofar as improving the quality of auditory inputs may reduce cognitive demands during listening in everyday activities. While there are data to support this for hearing rehabilitation, there are no data available on whether improving visual function through low-vision rehabilitation, specifically for reading, could have a similar protective or beneficial effect on cognitive health. Given that low-vision rehabilitation has been shown most effective for enhancing reading performance, the present proposal aims to **answer the following questions**:

- Does improved reading performance (reduced cognitive demand during reading) improve cognitive (memory) functioning in older adults with age-related vision loss?
- Is this effect equally strong in individuals who have visual impairment only, compared to those with dual vision and hearing impairments?
- Are age-related visual impairments at baseline and changes in reading performance following low-vision rehab, associated with changes in cortical architecture?

The Co-morbidity of Ocular Disease and Cognitive impairment

There is a growing body of evidence linking age-related eye disease such as macular degeneration (AMD) with changes in cognitive functioning and cognitive impairment due to Alzheimer's Disease (AD)[1–5]. The prevalence of AMD and AD increases with increasing age [6–9]; both conditions share many risk factors (e.g., smoking, obesity, age, and unhealthy diet [10]) and their co-morbidity has been reported to be higher than what would normally be expected if they were independent of each other [11–13]. Similarities exist between AMD and AD at the anatomical level, as both the brain and the retina are part of the central nervous system and are derived from the neural tube [14]. Histologic and immunologic associations have also been reported. Both the senile plaques of AD and the drusen deposits of AMD contain amyloid beta, clusterin, vitronectin, apolipoprotein E, and other inflammatory modulators, mediators and reactants, creating a similar pro-inflammatory microenvironment [15,16]. Studies point to chronic inflammation and oxidative stress, as well as protein accumulation due to decreased proteasome activity, as important causes of both diseases [10,17]. Studies have provided evidence that both the anatomical changes observed in AMD (e.g., drusen development in the retina) and in AD (e.g., formation of plaques in the brain) are symptoms of a common underlying disease mechanism within the central nervous system [16–18]. In addition, while AMD may not share a common origin with AD in terms of their genetic risk factors, many studies have reported an association with AMD and specific alleles of the APOE gene, a regulator of lipid transport also implicated in AD. While the E4 allele is associated with an increased risk of AD and the E2 allele is protective, the reverse is true for AMD [19]. However, transgenic mice expressing APOE4, the allele which increases the risk of AD, developed retinal features similar to AMD when fed a high-fat diet [20]. Beyond APOE, the T1277C allele of the CFH gene may predispose individuals to developing both AD and AMD [10], and there is early evidence that the p.Ala25Thr variant of CST3 is linked to both AD and wet AMD [21]. It is not surprising that there is also overlap between the behavioural aspects of AMD and cognitive impairment; for example, the presence of symptoms such as social disengagement and functional impairments may be present as a result or either or both conditions. Given this mixed evidence about possible causal and correlational links between both diseases, additional investigation is needed to explore the mechanisms underlying connections between visual and cognitive impairment and whether or not they can be modified by interventions.

Studying Sensory and Cognitive Loss – An International, National and Local Priority

Treatment and prevention options for cognitive impairment have become a central focus and priority for all stakeholders in health care research around the globe. In Canada, the Senate Report on the need for a Canadian Dementia Strategy was released in 2017[22] and resulting recommendations started to be rolled out in 2019[23] . These initiatives specifically refer to the importance of vision and hearing health research and the role of the Canadian Consortium on Neurodegeneration in Aging (CCNA). Of the 20 CCNA teams, *Team 17 (Interventions at the Sensory and Cognitive Interface*: *Implications for Communication and Quality of Life*; http://ccnateam17.ca/), is co-led by Wittich who will also lead the team for the proposed research. Internationally, a very recent publication in *The Lancet* [24] described cognitive impairment as the most challenging threat to population health in our century, and pointed out that **hearing loss** may be the largest modifiable risk factors for cognitive impairment . **Low Vision rehabilitation** (e.g., magnification strategies and reading rehabilitation) is ominously absent from this review paper; however, there is simply a lack of evidence from longitudinal or intervention studies regarding the links between visual loss and cognitive impairment. Some studies have indicated that improvement of vision through cataract surgery has resulted in improved cognition[25,26]; however, these results did not always replicate [27,28]. The main technique to improve visual input for reading in the presence of low vision has been magnification; however, vision rehabilitation has never been systematically evaluated using cognitive outcome measures. **The purpose of our proposed study is to fill this void by examining cognitive abilities in older adults before and after they undergo vision rehabilitation for reading.**

Low Vision (LV) Makes Reading More Effortful

The *Framework for Understanding Effortful Listening* (FUEL) can be used to illustrate how listeners may engage in effortful listening by allocating more cognitive resources to meet the demands imposed during listening in challenging conditions (such as when an individual has hearing loss and/or there is noise) [29,30]. Importantly, when some cognitive resources are diverted to listening, the remaining cognitive resources may be insufficient for listeners to rapidly or accurately comprehend or remember what was heard. The same logic can easily be applied to effortful viewing/reading to explain why the presence of central visual impairment has repeatedly been shown to reduce reading speed [31,32], specifically because processing of visual information in the retinal periphery is slower and not as efficient as in the macular region [33], in both younger and older observers[34]. In addition, low vision affects eye movements during reading, thereby shrinking the perceptual window where letters are processed, likely due to the increase in the cognitive demand[35].

Low Vision (LV) Rehabilitation Reduces Reading Effort

Overall, the effectiveness of LV rehabilitation has been demonstrated repeatedly [36,37]. A systematic review confirmed that there is strong evidence that low vision reading rehabilitation services improve reading ability overall [38], whether by using magnification devices (e.g., hand-held magnifiers, CCTVs, or zoom functions on an iPad[39,40]) or large print, with both methods having been shown to be equally effective [41]. Increasing reading performance (e.g. by increasing reading speed at decreased print size) is frequently the main target for improvement during rehabilitation, and it has been used as the primary outcome measure in recent clinical trials demonstrating the effectiveness of low vision treatments[38,42]. Clients with low vision can be trained to use either CCTV video magnifiers, or mechanical magnification devices (e.g., hand-help magnifiers, telescopes) to help improve reading performance by up to 200% [43]. Interestingly, the findings for reading comprehension in the presence of low vision are mixed [44], as reading speed (as a measure of effort), scotoma size, and visual acuity all influence comprehension, creating a potential breaking point at which comprehension by people with low vision is dramatically reduced when compared to comprehension by readers who are normally sighted. However, most of these studies are small and underpowered. Therefore it is hard to control for these factors, a problem we hope to overcome in our proposed project.

The Link between Reading and Cognition

Reading is a complex process that involves bottom-up visual processing to enable grapheme recognition that in turn enables grapheme-to-phoneme conversion, leading to word recognition and the identification of morpho-semantic, syntactic and conceptual features of lexical items that ultimately results in sentence and discourse comprehension of complex texts such as stories[45]. Because reading is subserved by a number of cognitive processes, including attention, memory and working memory,

there is a symbiotic relationship between reading and cognitive processing as has been documented extensively in the psycholinguistics/neurolinguistics, epidemiological and imaging literature [46,47]. Notably, a number of studies have shown that engaging in high-level cognitive activities, such as reading discourse, appears to preserve cognition. The frequency of participation in activities that are mentally stimulating, such as reading, is associated with lower risk of incident Alzheimer's disease[47–49]. More recently, studies have also linked reading and engaging in higher-level cognitive activities with increased cognitive reserve, that in turn is associated with more tolerance of AD pathology and stimulation of brain plasticity [50–53].

Structure-Function Relationships

Recent evidence suggests that visual field loss is associated with neuroanatomical changes in the brain, offering some interesting insights on vision-related brain plasticity. For instance, peripheral vision loss was associated with cortical thickness (CT) decrease in dorsal area V3d, early visual cortex (V1&2) and ventral area V4, while central vision loss was associated with CT decrease in V3d and V3A[54]. The mechanisms responsible for these changes, however, remain unclear. Prins et al. [55] showed that there was a decrease in gray matter volume in the bilateral superior lateral occipital cortices in a group of monocular blind patients when compared to a group of healthy controls, but that there were no volumetric differences in their visual cortex. These results are consistent with a functional deprivation hypothesis, rather than a trans-synaptic degeneration hypothesis, since the superior lateral occipital cortices play an important role in depth perception, and early visual cortex was spared [55]. Another study compared CT in 10 patients with macular degeneration (MD) to healthy controls [56]. Despite the small sample size, results indicated that MD participants had significantly reduced CT in centrally-responsive primary visual cortex, but interestingly that they had increased CT in peripherally-responsive primary visual cortex. This suggests that compensatory recruitment of spared peripheral vision may induce cortical thickening in specific areas of the visual cortex [56], a finding that would support the idea of improved function (e.g., reading) using the peripheral retina for reading after the development of AMD. Taken together, these results highlight the potentially important mechanisms of brain plasticity following visual loss, but they need to be replicated using a larger sample. Importantly, these results also open the crucial question of whether vision rehabilitation therapy may induce even more important changes in brain plasticity. To our knowledge, this question has never been addressed before. Therefore, the general **neuroimaging objectives** of this project will be 1) to investigate if visual impairment is associated with reduced cortical thickness in specific cortical areas at baseline (cross-sectional portion), and if vision rehabilitation will result in changes in cortical thickness after 12 months (longitudinal portion).

Does Reduced Reading Effort allow for Increased Reading Activity, Leading to Improved memory/cognition?

Pilot data from our currently funded FRQS project focusing on cognition and AMD indicate correlations between sensory and cognitive variables in the expected directions insofar as individuals with faster readings speeds demonstrated better scores on the Montreal Cognitive Assessment[57,58]. Given the information reviewed above, the logical direction for our investigation into the functional connection between LV and cognition is to examine the possible effects of reading rehabilitation on the cognitive abilities of LV patients over time. In order to dis-entangle the effects of visual and cognitive impairments in order adults, members of this research team have adapted cognitive tests so they can be administered to individuals with low vision [59,60]. In parallel, we are also in the process of developing a vision-screening test that can be administered to individuals with various levels of cognitive impairment [61,62]. This investigation will guide our future research efforts into the improvement of service provision in LV rehabilitation for the purpose of increasing the independence and health of older adults living with LV.

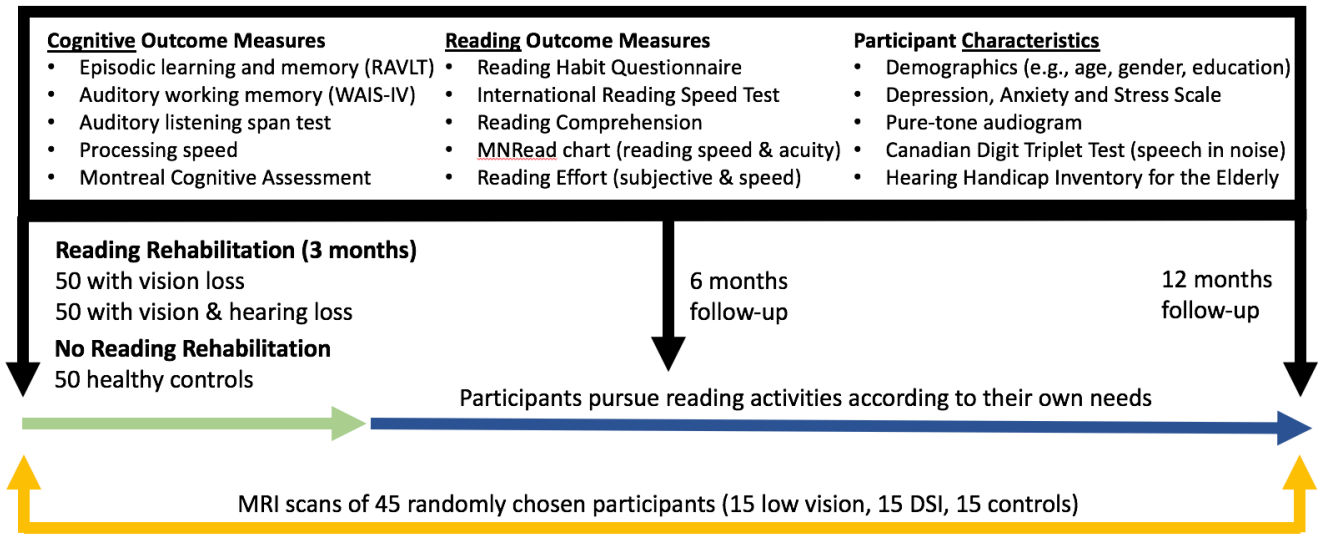
The objectives are to:

- Evaluate cognitive functioning and memory before, and 6 and 12 months after low vision reading rehabilitation using magnification in AMD patients, compared to those with dual (vision and hearing) impairments, and age-matched controls
- Correlate participant characteristics with all cognitive outcome variables in order to identify potential mediators, moderators or confounders

Hypotheses:

- Measures of reading effort (self-report and objective reading speed) will be statistically significantly reduced after participants have received strategies and tools to facilitate reading.
- Measures of reading behaviour will be negatively correlated with measures of reading effort (e.g., participants who report less effort will read a greater amount, more frequently and for longer)
- Individuals who demonstrate reduced reading effort and improved reading behaviour will demonstrate improved scores on cognitive tests after 6 months of having received rehabilitation strategies and tools, compared to those whose reading effort remains high or whose reading behaviour remains unchanged. These beneficial effects will be maintained after 12 months.
- Reading measures correlate with cortical thickness (CT) in the visual cortex;
- There will be reduced CT in the visual cortex in the low vision groups compared to matched controls at baseline
- Reading rehabilitation results in increased CT in the low vision groups, but not in the control group after 12 months.

Ethics Approval has been obtained through the *Comité d'éthique de la recherche* of the *Centre de recherché interdisciplinaire en readaptation du Montreal metropolitain (CRIR#1284-1217)* which is responsible for research protocols involving recruitment from the clinical partners (local sensory rehabilitation centres) within this study: the *CRIR/Centre de réadaptation MAB-Mackay du CIUSSS du Centre-Ouest-de-l'Île-de-Montréal*, and the *CRIR/Institut Nazareth et Louis-Braille du CISSS de la Montérégie-Centre* (see attached letters of support). Additional approvals and modifications (MRI component) will be obtained through the univerisiy affiliations of the team members.



Study Design: We will employ a quasi-experimental approach (non-randomized, pre-post intervention study)[63], an approach frequently used during the evaluation of health interventions [64]. Specifically, a 3x3 design (3 groups x 3 time points) will allow us to examine whether cognitive performance will change before and after 6 and 12 months of a low vision reading intervention, when comparing LV and dual sensory impaired (DSI) patients to age-matched controls with age-normal vision and hearing[65]. Participants will be audio-recorded throughout several of the tasks to ensure the highest level of precision when inputting and analysing data, and to help reduce the overall testing time. All aspects of the study design and data analysis will be submitted as a stage 1 pre-registered report.

Participants: We will recruit 150 new clients (65+ years of age) referred for low vision rehabilitation to either of the two vision rehabilitation centres in Montreal (Lethbridge-Layton-Mackay and INLB, see partner letters of support), and 50 age-matched (by decade) older adults without visual impairment (to be recruited from spouses or family members of particiapnts, as well as through open advertisement through media and senior groups). In addition, we have access to the *Banque des participants* of the *Centre de recherche institut universitaire de geriatrie de Montreal* (CRIUGM; n > 1000). Within this database, it will be possible to match our control participants on variables such as age, gender, education, and other potential variables of interest such as MoCA score). Client-participants are

required to have a diagnosis of AMD (any type), not currently be undergoing any medical treatment for their AMD (e.g., anti-VEGF injections) and must potentially benefit from a magnification intervention for the purpose of improving their ability to read. This reading intervention requirement (see description in data collection section below) will likely result in a large number of eligible participants as reading has been reported to be the number 1 complaint of individuals seeking vision rehabilitation[66]. Participants need to be able to communicate in either English or French, and have a visual acuity in the better eye of 20/60 or less with best standard refraction, according to the admission criteria for eligibility for rehabilitation services in Quebec [67]. DSI participants are eligible with an additional unaided pure-tone average (PTA) hearing loss across 4 frequencies (0.5, 1, 2 and 4 kHz) between 26 dB and 70 dB[68]. Those with a PTA >= 70 dB HL in their better ear are likely to have severe problems in speech communication, and will be excluded from recruitment. Based on past experience, because we will recruit participants over the phone, those with more severe degrees of hearing impairment would unlikely be recruited for the project. Progress of our pilot study[57,58] indicates that we will be able to recruite at least 3 AMD participants per week, making the recruitment goal feasible within 18 months. Given the familiarity of the team members of working with this population, it is our experience that recruitment is most successful when we offer the choice of coming to the lab space at either rehab centre or to be visited in their home for data collection (except for the MRI sub-study, whose participants will be randomly recruited among study participants). Therefore, informed written consent will be obtained and data will be collected either in the home or the lab at the first in-person meeting, and the procedures are developed accordingly to be easily portable.

Measures: The study includes outcomes measures of vision (e.g., reading), cognition (e.g., memory) and cortical architecture (MRI sub-study), as well as potential descriptors, clinical data and co-variants (e.g., hearing, demographics, depression etc.)
Cognitive Outcome Measures: We will investigate the potential effect of reading rehabilitation on three relevant areas of cognitive function. The first will be episodic learning and memory, assessed using the Rey Auditory Verbal Learning Test (RAVLT)[69]. Second, we will assess two aspects of auditory working memory: a) general auditory working memory and will be assessed using the WAIS-IV Letter Number Sequencing task[70] and b) an auditory listening span test, which will be a variant of the reading span task originally developed by Daneman and Carpenter[71] (a task highly associated with reading skill). The third domain is processing speed, and will be assessed using a computerized audio-visual choice reaction time task. Lastly, we will be assessing cognitive impairment using the adapted version of the Montreal Cognitive Assessment (MoCA)[59,72] for persons with visual impairment, should their visual impairment be too severe to administer the visual items. This measure will provide additional information regarding the participants' cognitive abilities, and help to identify possible cognitive impairment. These measures were chosen because they cover a wide range of cognitive functions, they are all **administered in the auditory domain** and thus will not be affected by a visual impairment, and have good psychometric properties. In other words, should performance on these cognitive measures improve following the vision rehabilitation program, the improvement will be attributable to the benefit of increased visual function on cognitive stimulation as opposed to merely being due to improved perception of the stimuli involved in the tests. Their administration can be **adjusted to make instructions audible** for persons with concurrent hearing loss. Moreover, they assess cognitive domains that have been shown to predict everyday function in older adults: episodic learning and memory[73], processing speed[74], and working memory[75]. In addition, we have aimed to harmonize as many of our cognitive measures as possible with those utilized in the Canadian Longitudinal Study on Aging, in order to increase the possibilities to compare our findings to that larger data set for 30,000 Canadians for whom baseline and first follow-up data are available[76].

Reading Outcome Measures:
To subjectively assess reading effort, we will administer a reading habit questionnaire, a measure developed specifically to evaluate the extent and frequency to which an individual engages in reading activities during their activities of daily living, including reading for entertainment or education. This measures has previously been employed by our team[39] and includes questions on language background (e.g., mother tongue, language proficiency), assessed self-reported proficiency in reading (1=no ability, 5=fluent ability), and reading habits before and after onset of low vision (e.g., frequency, enjoyment, type of reading). In addition, participants will be asked to read English or French paragraphs from the

International Reading Speed Test (IReST)[77]. It includes reading comprehension questions that have previously been developed and used in our lab in the context of a low vision reading evaluation using the iPad as a magnification device [39]. They will also read the English or French version of the MNRead chart [78], a clinical assessment chart that allows for the measurement of reading acuity (smallest print read), reading speed (in words per minute), critical print size (smallest print at which reading speed is still optimal), and the Reading Accessibility Index[79], which considers reading ability over a range of print sizes. Finally, we administer a primed lexical decision task where the participant first reads a sentence (prime) and then decides on a word (target) as quickly and as accurately as possible. This task evaluates reading speed, vocabulary comprehension and ability to judge content congruency[80,81].

Measures of Participant Characteristics

Depression, Anxiety, Stress: Not surprisingly, the onset of age-related vision loss due to AMD is often accompanied with a multitude of emotional responses that can potentially interfere with the success of low vision rehabilitation. Therefore, the Depression, Anxiety and Stress Scale [82] will be included in the protocol in order to identify individuals whose rehabilitation outcomes might be influenced by their psychological state. This 21-item questionnaire shows exquisite psychometric properties and has been validated in both English and French [83].

Hearing Assessment: Given that the cognitive assessment is designed in such a way that vision is not required for the administration of the testing materials, and given that the influence of **hearing** loss has been associated with the measurement of cognition [e.g., 84] and has been identified as a risk factor for cognitive impairment [24], hearing ability will be assessed as part of the protocol. In order to be able to consider hearing ability and listening effort during the cognitive assessment [29], participants will complete a pure-tone audiogram with a portable audiometer (Maico MA41 from GénieAudio), using Radioear DD45 earphones, to establish a mean unaided decibel hearing loss (dB HL) threshold across 0.5, 1, 2, and 4 kHz in each ear. We will document the ambient sound levels during testing, using the Decibel X app by SkyPaw Co. Ltd., because testing may be conducted in participants' homes. Ambient noise levels can then be used to statistically control for potential noise effects on hearing thresholds. For individuals who experience difficulties in hearing the experimental protocol instructions, we will have a Williams Sound Pocketalker (https://www.williamssound.com/pocketalker) on site in order to provide personalized amplification. In addition to pure-tone audiometric thresholds, speech-in-noise thresholds will be measured using the Canadian Digit Triplet Test in either English or French [85]. Participants will complete the Hearing Handicap Inventory for the Elderly (HHIE) questionnaire and three individual questions about hearing ability which assesses their perception of difficulties with activities of daily living that require hearing [86]. These hearing assessments are the same as those that have been used or are planned for the Canadian Longitudinal Study on Aging (CLSA) [87], thereby allowing us to cross-reference and compare data from both studies and optimize our ability to place our intervention findings in a larger Canadian context.

Clinical Variables: As part of any low vision exam, the eye care professionals within each of the rehabilitation centres record key variables in the patients' charts that will be available for extraction by the research team as part of their study consent. They include, but are not limited to: diagnoses (ocular and otherwise), monocular and binocular visual acuity (distance and near), contrast sensitivity, visual field diameter, type and duration of rehabilitation services provided (e.g., computer rehab, orientation & mobility services), type of assistive devices that were prescribed and provided (please note that these devices are free loans for life through Quebec Health Insurance/RAMQ; therefore, income is not a barrier to device use). The file contains information about the type and intensity of vision rehabilitation strategies that were implemented and trained (e.g., provision of improved lighting, strategies to read while placing materials on reading stands at the appropriate distance). In addition, the file contains basic demographic information (e.g., gender, age, living situation). These clinical variables will be available to the research team for the purpose of comparison, as well as statistical control and analysis.

MRI Acquisition – Subsample of 45 Participants (15 VI, 15 DSI, 15 control)

Imaging data will be acquired using a 3T Siemens Prisma fit MR scanner (Siemens, Erlangen, Germany) at the *Unité de neuroimagerie fonctionnelle of the Institut universitaire de gériatrie de Montréal*. High-resolution T1-weighted images will be acquired using a magnetization-prepared rapid acquisition with gradient-echo (MPRAGE) sequence, with the following parameters: TR=2.4 s,

TE=2.33 ms, TI=979 ms, flip angle=9 degrees, FOV=230x230, voxel size: 0.8 mm x 0.8 mm x 0.8 mm. Additional FLAIR, resting-state and DTI sequences will also be included as exploratory measures. Total acquisition time will last < 30 minutes plus 15 min instruction and preparation.

MRI image analysis: Cortical reconstruction will be performed using FreeSurfer (version 6.0.0)[88,89]. The following method uses both intensity and continuity information from the entire three-dimensional magnetic resonance volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the grey matter-white matter boundary to the grey-CSF boundary at each vertex on the tessellated surface [90]. Maps of cortical volume and cortical surface area will also be generated for exploratory purposes. Briefly, this processing includes motion correction [91], removal of non-brain tissue using a hybrid watershed/surface deformation procedure [92], automated Talairach transformation, and segmentation of the subcortical white matter and deep grey matter volumetric structures[93,94]. This is followed by intensity normalization [95], tessellation of the grey matter-white matter boundary, automated topology correction[96,97], and surface deformation following intensity gradients to optimally place the grey matter-white matter and grey matter-CSF borders at the location where the greatest shift in intensity defines the transition to the other tissue class[89,90,98]. Once the cortical models are complete, a number of deformable procedures can be performed for further data processing and analysis including surface inflation[99], registration to a spherical atlas, which is based on individual cortical folding patterns to match cortical geometry across subjects, parcellation of the cerebral cortex into units with respect to gyral and sulcal structure [100,101], and creation of surface-based maps of CT. The maps produced are not restricted to the voxel resolution of the original data, thus are capable of detecting submillimeter differences between groups. Procedures for the measurement of cortical thickness have been validated against histological analysis[102] and manual measurements[103,104]. The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. Cortical maps will be smoothed using a 20-mm FWHM Gaussian smoothing kernel. Images will be inspected and pial and white matter surface errors will be manually corrected. Figures will be created using Qdec included in the FreeSurfer distribution.

Sample Size: Effect sizes in vision rehabilitation in the past have ranged from approximately Cohen's *d* = .20 to 2.5[38]. Since there are no existing effect size estimates for cognitive ability in the context of low vision rehabilitation, we are applying these values as a guide line: Using an average value of d = 1.0, and converting this value into variance accounted for (r^2 = .20 [105]), we can estimate a required sample size. Using a 3x3 (group x time point) within-between design for Analysis of Variance, power analysis using gPower [106] indicates that a sample size of n = 141 allows us to detect small effect sizes of .15 or greater, with an alpha of 0.05 and a desired power of .95. We expected an attrition rate of around 10% at each time point, given our previous research with older visually impaired adults [107,108]. Therefore, a sample of n = 200 (to yield 150 patients, 50 controls) should be sufficient for our protocol. This goal is feasible given an average of 3000 new referrals to rehabilitation in Montreal per year.

Data Collection

Time 1 – Pre-Reading Rehabilitation: Participants will complete the questionnaires, hearing, reading and cognitive assessment components between their initial global intake exam and their first rehabilitation appointment. This period can span anywhere around 3 months, depending on waiting lists, and we will track whether any substantial changes in health occurred during this period that could influence eligibility or data collection.

The Low Vision Evaluation & <u>Reading Intervention</u> is delivered through rehabilitation services at the partner centers that are **regulated by the Quebec Ministry of Health**: Following Time 1 (within 3 months), participants will receive the full complement of services available and deemed suitable by their clinical staff and rehabilitation professionals of either rehabilitation centre. Both centres have a comparable service offer according to the provision of assistive devices and services regulated by the Quebec Health Insurance (RAMQ). These services are similar to those provided within the Blind Rehab Centers of the Veterans Affairs service offer in the USA [36,37] and include but are not limited to: a full optometric exam to determine functional vision, including refraction and the prescription of appropriate near and distance glasses and optical devices. This is followed by an assessment by a low vision therapist and/or occupational therapist that will establish the client's functional priorities and rehabilitation goals. They provide hand-held optical magnification devices, electronic non-optical

magnification devices (e.g., portable or table-top closed-circuit TVs), or computer software for screen content magnification (e.g., ZoomText). All are provided free of cost for the client and with appropriate training and follow-up sessions in the home within 3 months, if required. Participants may undergo a systematic lighting assessment [109,110] and may receive specific lighting recommendations that will improve their reading ability. In addition, clients will have access to referral services such as orientation & mobility training (for independent travel), registration for an adapted adult day centre for individuals with sensory loss[111], as well as the possibility to access psychosocial services, counsellors, social workers or other mental health professionals. The provision of assistive devices for magnification and reading is generally linked to a follow-up visit in the client's home 3 weeks after the initial rehabilitation appointment, in order to observe the use of the devices and strategies in the environment where the client lives. It is at this point that a decision is made with the client whether the devices are useful and will be assigned to the client as a permanent loan. Should additional needs emerge, the client is at liberty to contact the rehabilitation centre at any time to initiate a new service episode.
Time 2 – 6-Months and **Time 3 – 12-Months** Follow-Up: Six and 12 months after the initial rehabilitation appointment, the research assistant will meet with each participant (at home or in the lab, according to their preference) in order to repeat the experimental protocol, and all reading, cognitive and hearing measures will be administered each time. Throughout the period of the protocol, data from the rehabilitation chart will be extracted as it becomes available, with the final data collection concluding after the 12-month follow-up.

Statistical Analysis – Functional measures: To analyze these data, we will examine change in cognitive test scores from baseline over time using mixed-effects regression models, adjusting for level of vision and hearing impairment as fixed or random effects, and compare across sensory group (VI/DSI/Control). The analyses will include consideration of potential moderators or confounders (i.e., gender, age, education). In addition, we will calculate effect sizes, confidence intervals and Bayes Factors for main effects, interactions, and all post-hoc analysis.
When reflecting on the question of a control group we further consulted with the rehabilitation centres and discussed recruitment approaches and limitations; however, for practical and ethical reasons we are not able to withhold rehabilitation services from a possible comparison group, and waiting times are too varied across the centers and seasons of the year to allow for a waiting-list control group. As a result, we are proposing a quasi-experimental repeated-measures design with the intent to let the participants act as their own comparison across time points.
In addition, the data allow us to follow potential **exploratory avenues of analysis**:
1) If the recruited participants naturally divide into individuals whose reading effort was reduced and their reading activity has increased, versus those where we do not observe a change in reading behaviour, we can compare these two groups directly (e.g., while still considering their hearing status, or their gender)
2) If no such clear division occurs but participants naturally distribute along a continuum of reading effort and reading behaviour variables, we can simply use the reading measure(s) as co-variates to test whether any/all of the reading effort measures emerge as significant co-variates, and examine whether cognitive scores improved over time across our three groups, after removing the effect of reading rehabilitation success.
3) Finally, we will use **latent factor analysis** to explore whether specific clusters of variables are specifically associated with improvements in cognitive functioning and/or improved reading ability. This analysis will be led by Swenor, together with Johnson and Wittich.

Statistical Analysis - Cortical thickness:
Regression analyses of visual impairment on cortical thickness will be investigated at each vertex of the cortical surface using general linear modeling. Cortical thickness will be modeled as a function of group by controlling for the effects of age, gender, and education. Resulting clusters will be considered significant at $p<0.05$ using a Monte-Carlo simulation approach. Similar analyses will be performed for cortical volume and cortical surface area, with the addition of total intracranial volume as a nuisance factor[112]. In addition, a region-of-interest approach will be used to extract the CT values in specific regions of interest using the Destrieux cortical atlas[113] in FreeSurfer. More specifically, we will compare across groups CT values extracted within specific regions of the visual cortex including the

inferior occipital gyrus, the middle occipital gyrus (and sulcus), the superior occipital gyrus, the cuneus, the lingual gyrus, the occipital pole, and the calcarine sulcus. CT will be investigated more specifically inside visual areas, namely V1 (BA17) – primary visual area, V2 (BA18) – secondary visual area, and V5/MT – visual area, middle temporal, by using an atlas from the Martinos Center for Biomedical Imaging (US) and the Institute of Neurosciences and Biophysics (Germany) (http://surfer.nmr.mgh.harvard.edu/fswiki/BrodmannAreaMaps). In order to examine if vision rehabilitation will result in changes in CT, we will examine by calculating percentage difference in extracted CT values for each of the above-mentioned visual regions pre- and post- reading rehabilitation. Differences between groups or between regions pre- and post-intervention will be considered significant at $p<0.05$ after correction using false discovery rate.

Limitations & Mitigation Strategies:
Given the logistics of having the reading intervention delivered through services that are regulated by the Quebec Ministry of Health, we place our trust in the quality of rehabilitation service delivery without being able to control this aspect of the study; however, we believe that this trust is well deserved, given the quality and type of care provided in Quebec[114–116]. It is likely that a certain number of participants will self-select not to complete the 1-year follow-up or to abandon parts of the recommended intervention tools and techniques. Therefore, we will examine differences in participant characteristics and consider intent-to-treat within the statistical analyses. We expect certain variability in the cognitive status of our participants, as there are no cognitive exclusion criteria. This pragmatic approach to recruitment is chosen intentionally as we speculate that the beneficial effect of reading rehabilitation may become apparent at different levels of magnitude, depending on the cognitive starting point; however, this remains speculation at this point. Our statistical analyses will need to consider this additional source of variability.

Integrated KT strategy: Established collaborations with the Sense-Cog group in Europe (https://www.sense-cog.eu/), Envision University in the USA (https://university.envisionus.com/Home) and the CCNA KT team provide access to sensory-cognitive-specific KT networks that will facilitate the distribution and implementation of our findings. In addition, we have secured specific iKT collaboration with the Center for Interdisciplinary Rehabilitation Research of Greater Montreal (see support letter), Envision University and the annual Envision Conference in Wichita, Kansas (see support letter). Swenor, as a visually impaired scientist[117] and a team member brings a unique and important KT, equality and inclusion perspective to the project. Our close partnerships to local sensory rehabilitation agencies (represented by Lizé and Maynard) allow for an ongoing exchange to ensure that the project development remains clinically relevant while allowing us the expand sensory-cognitive health science (see also Wittich lab network in Appendix). All collaborators and partners will participate in the development of a *Café scientifique* at project completion in order to disseminate the results at a clinical level. In addition, dissemination and continuing education courses will be developed for Envision University online as well as for Envision Conference in person.

Sex, Gender, Equity, Diversity & Inclusion: Being female has been identified as a risk factor for the development of AMD in some[118] but not all studies[119]; therefore, self-reported gender (binary men/women) will be considered in all analyses for comparison and as a control. We will pay specific attention to the men/women ratio in the sample as recruitment will likely result in a larger number of women who will participate, given their increased lifespan and larger client numbers in vision rehabilitation settings. In addition, contradicting gender differences in openness to the acceptance and use of assistive technology have been reported [120–122], which directly impacts on the potential benefit of reading rehabilitation approaches that include electronic magnification (e.g., the use of an iPad[39,40]). Therefore gender will feature prominently in our statistical analyses.
The team composition is roughly gender-balanced (6 women, 4 men). Equity and diversity are important to all team members: the team leader is a first-generation allophone immigrant and member of the LGBTQ2S community; one team member is a visually impaired scientist and advocate for disability in science, and eight team members are fluently bilingual English/French of whom 3 are native francophones. We have extensive experience supervising graduate students with disabilities (specifically those with visual, hearing and/or motor impairments) given the increased interest of this student population in the topic of disability and accessibility.