Prevention of Alzheimer's Dementia with Cognitive Remediation plus Transcranial Direct Current Stimulation in Mild Cognitive Impairment and Depression (PACt-MD)

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Final Protocol

TITLE:	Prevention of Alzheimer's Dementia with Cognitive Remediation plus Transcranial Direct Current Stimulation in Mild Cognitive Impairment and Depression (PACt-MD)
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Title: Prevention of Alzheimer's Dementia with Cognitive Remediation plus Transcranial Direct Current Stimulation in Mild Cognitive Impairment and Depression (PACt-MD)

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I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the International Conference on Harmonization / Good Clinical Practice.

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1.1 Objective and Specific Aims

1.2 Abstract:

By the time Alzheimer's Dementia (AD) and related disorders (ADRD) are diagnosed the brain has sustained substantial insult that limits the efficacy of current treatments. Preventive interventions are urgently needed but prevention studies require large numbers of participants and long follow-up periods unless they can target a high- risk population.

We propose to study the efficacy of a preventive intervention for AD in three high risk groups: (1) older persons with Mild Cognitive Impairment (MCI); (2) older persons with a major depressive disorder (MDD), (as indicated by a past major depressive episode (MDE)), without MCI; and (3) older persons with a MDD and MCI. MCI is considered a prodromal condition for dementia with a progression rate of about 1% per month. Depression has independently been identified as one of the most promising targets for AD prevention studies, as, even after successful treatment of their depressive episode, older depressed participants develop MCI or dementia at a rate of 1-2% per month. Having a MDE at any time during adult life statistically significantly increases the risk for dementia in late life. Several studies have compared the risk of developing dementia and its association with a MDE occurring in mid- vs. late-life and observed mixed results. Of these studies, some found that the risk of dementia is higher in older adults with a MDE in mid-life; some found that the risk is higher in those with a MDE in late-life, and some found that the risk is similar regardless of when the MDE occurs. In addition, a large epidemiological study has shown that having been treated with an antidepressant at any time during one's adult life and for any duration is associated with an increased risk for dementia. Paradoxically, brief remote exposure to an antidepressant appears to be associated with a higher risk for dementia than a prolonged recent exposure.

Our proposed intervention is a combination of cognitive remediation (CR) and non-invasive brain stimulation – transcranial Direct Current Stimulation (tDCS). Participants with MCI or a MDD (with or without MCI) will be randomized to tDCS + CR or sham tDCS + sham CR. Both CR and tDCS have been shown to induce neuroplasticity and improve cognition. We hypothesize that their combination will enhance cognitive reserve and protect against cognitive decline.

Our design is informed by our experience conducting randomized controlled trials (RCTs) in older participants with dementia, MCI, or MDD over more than two decades. In our recent donepezil prevention trial, combining donepezil with standard antidepressant maintenance prevented cognitive decline and the incidence of dementia in participants who had both a MDE in late life and MCI. Building on this prevention trial, we conceptualize the proposed study as a high-risk, high-gain RCT aimed at enhancing cognitive reserve and preventing cognitive decline and dementia in a high risk population. If we are successful in this high risk population, then tDCS + CR can be tested in, and extended to, the general population (i.e., for universal prevention) or other groups at high risk for AD (i.e., for selective or indicated prevention).

Five Toronto academic sites with a history of successful collaboration will consent up to a total of 500 participants meeting criteria for MCI (age 60 and older) and MDD (age 65 and older) to reach a target of 375 enrolled participants initiating the study intervention. Where a MDD is defined as one or more MDE(s) that

occurred during the participant's adult life (i.e., they must have been 18 years of age or older at the time of the MDE). For a MDE(s) with an offset date that is more than five years from the time of the study screening visit, the participant must have received medical attention (see below) for at least one of their MDEs. For a MDE(s) with an offset date of two months to five years from the time of the study screening visit, medical attention for the MDE is not required. Participants will be randomized under double-blind conditions to either: i) tDCS + CR or ii) sham + sham. They will first receive tDCS + CR (or sham + sham) 5 days a week for 8 weeks, followed by home-based CR (or sham) and booster sessions of tDCS + CR (or sham + sham) for 5 days every 6 months and followed for 24-84 months, until they develop dementia (or MCI for those who are deemed cognitively intact at baseline) or complete the study.

1.3 **Objectives:**

By the time Alzheimer's Dementia (AD) and related disorders (ADRD) are diagnosed the brain has sustained substantial insult that limits the efficacy of current treatments. Preventive interventions are urgently needed but prevention studies require large numbers of participants and long follow-up periods unless they can target a high- risk population. We propose to study the efficacy of a preventive intervention for AD in three high-risk groups: (1) older persons with MCI; (2) older persons with a MDD without MCI; and (3) older persons with a MDD and MCI. MCI is a significant risk factor for developing AD; while the annual incidence of AD in the community in people > 65 years of age is 1-2%/year, in individuals with MCI it is up to 15%. Currently there is no pharmacological or non-pharmacological intervention that has demonstrated efficacy at reducing or delaying the development of AD in those with MCI. Thus, this high risk, untreated population represents an excellent and urgent target for a novel preventative intervention.

In a 2010 report from the National Institutes of Health (NIH), depression was identified as one of six potentially modifiable risks for cognitive decline, AD, or both (the five others were diabetes mellitus, present smoking, cognitive inactivity, physical inactivity, and diet with high saturated fat and low vegetable intake)[1]. A subsequent Lancet Neurology review[2] calculated that successful interventions targeting depression could reduce the prevalence of AD by up to 15% in North America, making depression the second most promising target for prevention studies after physical inactivity. However, our and others' data have shown that even after successful treatment of depression, older participants still show cognitive deficits[3-6] and develop MCI or dementia at a rate of 1-2% per month[3, 7, 8].

Our proposed intervention is a combination of cognitive remediation (CR) and non-invasive brain stimulation – transcranial Direct Current Stimulation (tDCS) – in participants with MDD (with or without MCI) or with pure MCI. All participants will be randomized to tDCS + CR or sham tDCS + sham CR ("sham + sham"). CR enhances frontal lobe activation and neuroplasticity[9] and it has been shown to improve cognition in depression[10-12]; tDCS modulates neuronal activity and enhances neuroplasticity[13] and it has been shown to improve cognition in mild AD[14-16]. We propose to combine CR and tDCS to optimize CR effects on neuroplasticity through tDCS neuromodulation. We hypothesize that through this synergistic effect, tDCS + CR will improve and maintain cognition in participants with MDD or MCI, thus preventing the incidence of dementia in those with MCI or of MCI in those who are cognitively normal.

Our design is informed by over two decades of experience conducting randomized controlled trials (RCTs) in older participants with dementia or a MDD. In our recent donepezil prevention trial, combining donepezil with standard antidepressant maintenance prevented cognitive decline and the incidence of dementia in participants who experienced a MDE in late-life[8]. However, donepezil also caused severe mood symptoms

in many of these participants supporting the need for a different preventive intervention. We conceptualize the proposed RCT as a high-risk, high-gain attempt to enhance neuroplasticity and cognitive reserve to prevent dementia in three high-risk groups. If we are successful in this population, tDCS + CR can then be tested in, and extended to, the general population (i.e., for universal prevention) or other populations at high risk for AD (i.e., for selective or indicated prevention).

1.4 **Specific Aim and Hypothesis:**
The two **primary aims** are to compare the efficacy of tDCS + CR vs. sham + sham in participants with a MDD (with or without MCI) or pure MCI in (1) preventing long-term cognitive decline (Aim 1) and (2) preventing the incidence of dementia (or MCI) (Aim 2). A **secondary aim** is to assess whether tDCS + CR improves cognition acutely.

In addition, exploratory aims will assess the moderating effects of several biomarkers (e.g. peripheral biomarkers (e.g., BDNF), genotype, and neuroimaging measures) on tDCS + CR effects.

Hypotheses: Compared to sham + sham, tDCS + CR will significantly slow down long-term cognitive decline (H1); reduce the progression of those with MCI to dementia (and of those who are cognitively normal to MCI or dementia) (H2); acutely improve cognition (H3).

2.0 Background and Significance

Focus on participants at high-risk for AD

(1) Participants with MCI. We will enroll participants who meet DSM 5 criteria for Mild Neurocognitive Disorder. While all participants will undergo genotyping for ApoE allele carriage and other genes that have been identified as risk factors for cognitive impairment, dementia, and depression outcome, we chose enrolment based on clinical criteria rather than biomarker-based criteria because most MCI in Canada will be diagnosed by clinicians using clinical criteria - Biomarkers such as CSF, ApoE allele status, specialized EEG, or quantitative MRI measures are not necessarily recommended at the present.
(2) Participants with MDD: Participants with MDD are an ideal group to conduct an RCT of secondary prevention of ADRD for the following reasons: first, MDD is prevalent and many participants with MDD seek treatment, thus they can be recruited and retained in long-term RCTs (see Preliminary Studies) at a higher rate than in studies enrolling participants with pure MCI or mild AD[17]. Second, preventing recurrence of MDD is already well established and can be offered "in the background", forming a structure for the retention of participants for an AD prevention RCT. Finally, even with successful treatment of MDD and prevention of its recurrence, older participants with MDD remain at high risk for dementia and about half already suffer from MCI, thus most are motivated to receive an intervention that may prevent ADRD (see Preliminary Studies below).

MCI. As an intermediate state between normal cognition and incipient dementia, MCI represents the highest known clinically identifiable risk-indication of non-familial Alzheimer-type dementia; the incidence of AD in the community in people >65 years of age is 1-2%/year, whereas in individuals with MCI the risk is up to 15%. While clinically established, no therapies exist to treat MCI symptomatically or to slow its progression to dementia. Thus, individuals identified as having MCI constitute the most important at-risk

population for developing AD, and represent a critical participant population for prevention of further progression of disease.

MDD and Dementia. Depression has been identified as the second most promising modifiable risk factors for ADRD after physical inactivity[2]. In two meta-analyses, a life-time history of depression doubles the risk of AD[18, 19]. A recent depressive episode (i.e., within 10 years) increases the risk of dementia or AD 4-6 fold[20, 21]. Among non-demented older participants with MDD and cognitive impairment, progression rates to dementia are 30-45% over follow-up of up to 3 years[3, 8] and > 50% over longer periods[7, 21].

MDD and MCI. The relationship between MDD and MCI is complex. In the CHS population-based study, 20% of MCI participants exhibited depression[22]. Conversely, in our and others' studies, 40-60% of non-demented older participants with remitted MDD qualify for a diagnosis of MCI: 44% of older participants with MDD in our donepezil prevention RCT[8] were diagnosed with MCI after having responded to antidepressant treatment and 33% of them progressed to dementia over the next 24 months. Of those who became demented, 83% were diagnosed with AD. The literature suggests that cognitive impairment in MDD is a form of MCI[2], which is a major risk factor or precursor to AD[23].

MDD and Cognitive Impairment. Cognitive deficits in non-demented older participants with MDD are highly prevalent and they lead to dementia in a large proportion of participants[7, 8, 21, 24]. They are mainly observed in information processing speed, executive function, attention and inhibition, and both verbal and visuospatial memory[4-6, 25-30]. Deficits in executive function and memory both increase the risk of depression relapse during antidepressant maintenance[25] and predict progression to dementia[21, 24].

Rationale for CR: Cognitive-behavioural therapy or problem-solving therapy improves depressive symptoms but they do not directly target cognitive deficits and there is no published evidence that they improve them in MDD[33]. By contrast, CR addresses cognitive inactivity- one of the six identified major modifiable risk factors for AD[1] and it enhances executive function and memory, both highly relevant to cognitive decline and progression to ADRD in MDD (see above). CR has been shown to improve cognition in schizophrenia[34], bipolar disorder[35, 36], alcohol dependence[37], and major depression[10-12].

Table 1: Controlled Trials of CR in Major Depression: Effect on Cognition[10-12].

Ref.	N (mean age ± SD)	Frequency and duration of CR	Results	Median ES
10	24 (50.3 ± 6.4)	2/wk x 10 wks	Verbal memory and attention	0.54
11	16 (33.6 ± 11.2)	2/wk x 10 wks	Verbal learning and recall	0.45
12	33 (49.2 ± 11.8)	1/wk x 10 wks	Verbal learning and memory Attention and processing speed	1.07 0.65

The third trial in depression[12] was led by Dr. Bowie, one of the team members. Its effect sizes (ES) were larger and it differed from the two previous trials by including not just computerized drill–based exercises but also strategic self-monitoring and bridging to real life. We propose to use this approach with the same computer exercises and therapist-based group sessions (see below). The rationale for using daily CR initially is two-fold. First, we are proposing that CR and tDCS will have a synergistic effect and tDCS will be administered daily (see below).Second, the amount of CR completed and cognitive improvement are correlated[12] suggesting that more frequent CR is likely to increase its effects. Thus, participants will also

performed computerized drill-based cognitive exercises at home daily for 20 minutes, between the therapist-led group sessions.

Table 2: Trials of tDCS in Mild to Moderate AD: Effect on Cognition[14-16]

Ref.	N (mean age ± SD or range)	Duration of tDCS and design	Results
14	10 (75.2 ± 7.3)	15-min session Anodal tDCS vs. sham	17% improvement in word recognition and discrimination
15	10 (70-92)	30-min session Left DLPFC or left temporal cortex vs. sham	Improvement in visual recognition memory: DLPFC: 18%; temporal cortex: 14%
16	15 (78.9 ± 8.2)	30-min session 1/day x 5 days to right & left temporal cortex vs. sham	Improved visual recognition memory that persisted for length of study (four weeks)

Rationale for booster: To date, all brain stimulation treatments that are used acutely (e.g., ECT, rTMS) require some form of long-term maintenance treatment, using either the same form of treatment (e.g., continuation/maintenance ECT or rTMS) or a different one (e.g., psychotropic medications or psychotherapy). Similarly, most preventive interventions typically require long-term courses regardless of whether a biological intervention is used (e.g., anticoagulants for the prevention of strokes[41] or a behavioral ones (e.g., diet and physical activity for the prevention of diabetes[42]. Thus, we believe that maintenance ("booster") sessions are necessary to maintain the expected effects of the initial 8-week intervention. Based on other maintenance and prevention models, we also believe that higher intensity and frequency would be more efficacious but also more burdensome. Thus, in the absence of data to guide the selection of the frequency or intensity of the maintenance intervention, we are proposing to study a 5-day "booster" every 6 months because 5 days allow us to repeat all the CR exercises and we do not expect that it will burden the participants and their family.

Rationale for tDCS: tDCS is a non-invasive brain stimulation method that can be safely administered to awake outpatients. It does not require general anesthesia or surgical implantation. It utilizes low intensity electrical current (e.g., 2 mA) either to increase cortical excitability with an anodal electrode or to suppress cortical excitability with a cathodal electrode[13]. Anodal tDCS improves memory in participants with mild to moderate AD when applied to the temporo-parietal cortex or left DLPFC[14-16]. These three studies suggest that even in AD, anodal tDCS improves cognition. Thus, we expect larger anodal tDCS effects among participants with MDD at high risk for AD but not yet demented. These and other studies also suggest that the priming effect of anodal tDCS could enhance the effects of CR administered shortly after tDCS.

Optimal Electrode Placement and Stimulation parameters:
Anodal tDCS has also been tested as a treatment for major depression[43,44]. In one recent RCT[44], 120

participants (mean age: 42 ± 12) with major depression were randomized to sertraline vs. placebo and active tDCS vs. sham using a 2x2 factorial design. During twelve daily 30-min. sessions, anodal tDCS (2 mA) was delivered to the left DLPFC and cathodal tDCS to the right DLPFC. Depression improved with tDCS, sertraline, or their combination but the combination was most efficacious. Also, prior to randomization, one session of bilateral tDCS with the same parameters enhanced working memory[45]. We plan to use similar tDCS parameters in our RCT. In another study, one session of anodal tDCS to the left DLPFC of 22 antidepressant responders (mean age: 32 ± 10) normalized deficits in cognitive control over emotional distractions during a working memory task[46]. These two studies suggest that tDCS improves cognition in participants with depression and targets the same function and structures as targeted by CR.

We plan to deliver excitatory stimulation bilaterally to the frontal lobes and in particular the left and right DLPFC. Based on simulation models, we will place the anode at Fz and the cathode at Iz to acheive this bilateral frontal excitatory stimulation. This is different than the left anodal and right cathodal tDCS as in the two studies that included participants with depression described above[43,44,46.] Rubber electrodes will be inserted in 35-cm^2 saline- soaked sponges and fixed with a headband. The direct current will be of 2 mA (current density = 0.57 A/m^2) for 30 min per day, just before the start of each CR group session.

The rationale of using bilateral frontal excitatory stimulation with a midline (Fz) anode is that anodal tDCS has been associated with enhanced cortical function while cathodal tDCS has been associated with reduction in cortical function[14]. In studies focused on acutely depressed participants, cathodal tDCS is delivered to the right and anodal tDCS to the left DLPFC as hyperactivity of the right DLPFC and hypoactivity of the left DLPFC are reported during acute depression[47-50]. In contrast, we will be administering tDCS to participants after they were successfully treated for an episode of MDD and are stable. These participants have been reported to have bilateral hypofrontality[51,52]. Hence, we chose to excite both the right and left DLPFC and consequently enhance DLPFC function and working memory. This approach is also relevant to the participants with pure MCI that we are now proposing to include: a course of daily bilateral anodal tDCS for 5 days in participants with mild AD has been shown to improve visual memory with a persistent effect of up to 4 weeks[53].

Sham tDCS will use the same parameters except that the device will be turned off after 1 min of active stimulation. This approach has been shown in other studies to be effective in ensuring that the participants are blind to the type of stimulation (active vs. sham) since this sham condition is associated with the common side effects of mild scratching and discomfort that are experienced immediately after stimulation is initiated[54,93].

tDCS and sham tDCS will be administered by certified technicians under the supervision of research physicians. Although tDCS is straightforward to apply, these technicians will complete a tDCS practical course before administering tDCS; they will also participate in assessments and courses at regular intervals to ensure that the administration of the intervention remains standardized throughout the study. These technicians will not be blind to the interventions but they will not be involved in any research assessment.

tDCS and Neuroplasticity

Animal studies support that tDCS has lasting effects on neuroplasticity[55] and that BDNF is a key mediator of this effect[56]. In healthy humans, anodal tDCS delivered to the DLPFC improves executive function and working memory [57-59]. When combined with working memory training, it enhances performance beyond working memory training alone[58]. This supports our rationale for combining tDCS with CR. Enhanced executive function to anodal tDCS to the DLPFC persisted for 12 months after stimulation[59], supporting long-

lasting neuroplasticity effects. The persistent effects of tDCS on neuroplasticity are also supported by neurophysiological studies[60], including a recent study using transcranial magnetic stimulation (TMS)-evoked EEG potentials[61]. Finally, this increase in neuroplasticity is proportional to the number of tDCS sessions[62]. Thus, we propose to use multiple sessions. In summary, animal and human studies support that tDCS increases neuroplasticity. Thus, we propose to combine tDCS with CR as we hypothesize that through its neuroplasticity effect, tDCS will prime the brain and optimize its response to CR.

Safety Profile

tDCS has previously been used in multiple studies involving older, frail participants with neuropsychiatric disorders such as AD, depression, Parkinson's disease, or stroke, with no adverse sequelae noted [63-65,53,44]. In our own experience, the procedure produces a mild tingling sensation initially which usually completely resolves within 30 seconds. In a study that systematically elicited side effects in 77 healthy controls and 25 participants who underwent 567 tDCS sessions[66], participants reported a mild tingling sensation (71%), moderate fatigue (35%), a slight itching sensation under the stimulation electrodes (30%), a mild headache (12%), nausea (3%), or insomnia (1%); only 18% as mildly unpleasant.

Compliance and User Experience

The investigators in this study have been involved in several clinical trials using brain stimulation that has required daily treatment as in the proposed study: over the past 7 years, they have successfully treated older participants with daily rTMS or tDCS for up to 6 weeks followed by various long-term maintenance protocols. In these studies, compliance issues did not interfere with the study scientific objectives. In general, we observe higher compliance with daily treatment in older adults than in younger ones since the majority of these older adults are not working. In the proposed study, participants will come on site for daily treatment with tDCS + CR or sham + sham. Thus, we will be able to monitor and support compliance with the core components of the intervention. We will also be able to monitor and support compliance with home CR exercise.

Why Targeting the DLPFC with tDCS?

Several lines of evidence suggest that the DLPFC provides neural substrate for cognitive reserve in participants with AD: it is hyperactive in healthy individuals who are carriers of ApoE4 during learning and recall[67]. It is hyperactive in participants with MCI during a semantic task[68]. Finally, amyloid plaques and thinning of micro- columns in the DLPFC of participants with mild AD are associated with decreased cognitive reserve rather than with cognitive deficits thought to be more specific of AD[69]. This is consistent with the compensatory role attributed to the prefrontal cortex in normal cognitive aging[70]. Given its capacity to experience neuroplasticity in response to injury[71], the DLPFC is thought to compensate for the cognitive effects of plaques and tangles in other regions of the brain (e.g., parahippocampus). In turn, accumulation of these plaques and tangles in the DLPFC compromises its capacity for neuroplasticity and results in cognitive decline and dementia [69]. Thus, we propose that enhancing neuroplasticity in the DLPFC with tDCS and CR will increase cognitive reserve, improve cognition, and alter the trajectory of cognitive deficits in participants with MDD**.**

Why tDCS rather Than Other Forms of Brain Stimulation?

Our team has experience in other forms of brain stimulation (i.e., ECT, MST, DBS, rTMS), some of which have shown some beneficial effects on cognition (e.g., rTMS, DBS). However, for this study, we chose tDCS because of: (1) the published data in both AD and depression (see above); (2) its tolerability and safety even in frail elderly; (3) its ease of use and low cost, increasing the likelihood that its use can be generalized (e.g., in primary care practice) if our RCT is successful.

Rationale for Biomarkers: We will collect biomarkers at T0 (including MRI at T0, T2, T9/Tx, and other*) to better characterize our participants and their risk for developing AD (or MCI). These analyses should be useful whether the RCT leads to positive or negative results: if results are positive, biomarkers analyses could identify mechanistic moderators. If results are negative (e.g., because of lack of power), we could still detect significant changes in biomarkers because of their lower variability and higher effect sizes than cognitive and diagnostic measures[72].

* Additional LP biomarkers will be collected prior to the LP procedure which can occur at any point in the study.

Table 3: Proposed Biomarkers and Brief Rationale for their Inclusion

Genotyping including ApoE status	Strongest genetic predictor for AD; vulnerability to stress associated with reduced hippocampal volumes and glucose hypometabolism[75]	T0
CSF biomarkers: a-beta 42, phospho-tau, and tau levels	Abnormalities in CSF may also identify participants who are in the pre-symptomatic phases of Alzheimer's Dementia[76,77]	T0
BDNF and other peripheral markers	BDNF lowered in depression and increased by antidepressant[78] lowered in AD[79]	T0, T9/Tx, other
Structural and volumetric MRI measures	Support diagnosis of AD vs. vascular dementia. Entorhinal cortex thickness and hippocampal volume predict dementia[80]; MDD associated with small temporal lobes [81] and smaller hippocampal volume[82,83]	T0, T2, T9/Tx
DTI measures	MDD with MCI associated with more frontal, parietal and temporal white matter atrophy[84]	T0, T2, T9/Tx
EEG	EEG will be used to study theta-gamma coupling during the working memory task ("N-back") as a probe of the DLPFC function. We will assess whether: (1) baseline theta-gamma coupling during N-back is a moderator of cognitive change in response to CR + tDCS; (2) change in theta-gamma coupling during N-back is a mediator of cognitive change in response to CR + tDCS. Working memory is a core cognitive function that we aim at improving with CR + tDCS.	T0, T2, T3..,T9/Tx

Rationale for Main Design Choices:

(1) In MDD, we will administer tDCS + CR (or sham + sham) only to the participants who have a history of a resolved MDE because we want to establish a stable baseline of cognitive performance and assess for MCI and rule out dementia after MDD response, without the confounding effects of a current depressive episode. The frequency of CR and tDCS during the induction phase is based on published results in depressed adults[44]. Based on our experience with brain stimulation trials[43], we are confident that participants with MDD can comply with 5 sessions/week for 8 weeks. The acute effect of this induction phase will be assessed at T2. The consolidation phase is based on the evidence of a dose/response relationship for both CR and tDCS (i.e., more sessions result in better effect) (see above). A 5-day "booster" every 6 months allows the repeat of all the CR exercises and we do not expect that it will burden the participants and their family.

2) Using progression from cognitively normal to MCI or MCI to dementia as endpoints is congruent with recent recommendations for AD prevention trials[2]. As in the donepezil prevention trial, rather than cut-off cognitive scores, we will use a consensus conference to determine whether participants meet diagnostic criteria for MCI or dementia at all assessment points (T0 and T2 to T9/TX). If participants meet criteria for any dementia at baseline or at T0, they will not be randomized since our aim is to study the prevention of dementia. Subsequently (i.e., after randomization), if a participant meets criteria for any dementia (or MCI for those who are cognitively normal at T2), this will be an informative endpoint. The consensus conference will take into account scores of the neuropsychological tests, CDR[89], and E-COG, and whether cognitive impairments represent a decline, are accompanied by functional decline, or are attributable to causes other than a dementia. This approach has high inter-rater reliability for dementia[89,90] and a high sensitivity (98%) and specificity (88%) for the diagnosis of probable AD[89,90]. It will ensure that participants receive appropriate diagnoses of MCI and dementia, maximizing their safety and protection.

Preliminary Studies: The proposed study is the continuation of a series of NIH-funded prevention studies of MDD, primarily in persons who experienced a MDE in late life. In 2 RCTs published in JAMA[86] and the New England J. of Medicine[85], antidepressant maintenance prevented the recurrence of MDD in young-olds[86] and old-olds with either an early-onset depression recurring in late life or a first ("late-onset") depression[85]. These RCTs also served as platforms to study cognition in MDEs which occurred in late life (see above). Failure both to normalize cognition and to halt its decline despite successful antidepressant maintenance led to a third RCT designed to test whether donepezil combined with long-term maintenance with citalopram (a SSRI) or venlafaxine (a Serotonin-Norepinephrine Reuptake Inhibitor – SNRI) would be superior to placebo combined with antidepressant maintenance to prevent cognitive decline and dementia in participants diagnosed with MDD in late-life[8]. To our knowledge, this trial remains the only published RCT to assess the prevention of cognitive decline and MCI or dementia in MDD, which presented in latelife: 130 (62%) of 209 non-demented participants with MDD aged 70 and older responded to acute open treatment with citalopram or venlafaxine and consented to be randomized; 57 (44% of those randomized) had MCI [amnestic: 35 (27%); non-amnestic: 22 (17%)] and 73 (56%) had "normal cognition." Donepezil temporarily improved global cognition, but ES were small (Cohen d=0.27). Donepezil was more likely than placebo to be associated with recurrence of a MDE (35% vs. 19%; HR = 2.09 [95% CI: 1.00-4.41]). Of the 27 participants with MCI on placebo, 9 (33%) progressed to dementia over 2 years vs. 3 (10%) of 30 on donepezil (p=0.05) [8: probable AD; 2: possible AD; 1: FTD; 1: other dementia]. In the MCI subgroup, depression recurrence rates were 12% with placebo vs. 44% with donepezil (LR=4.91; p=0.03). Of the 36 participants without MCI ("normal cognition") on placebo, 8 (22%) progressed to MCI[7] or dementia[1] over 2 years vs. 6 of 37 on donepezil (16%) [all progressing to MCI] (p=0.56). Among the 63 participants on placebo, 9 (13%) terminated the trial due to non- informative events (intercurrent physical illness, withdrawal of consent, etc).

3.0 Research Design and Methods

Summary: We will consent up to 500 participants meeting criteria for MCI (age 60 and older) and MDD (age 65 and older) in order to reach a target of 375 randomized participants initiating the study intervention, where a MDD is defined as one or more MDE(s) that occurred during the participant's adult life (i.e. they must have been 18 years of age or older at the time of the MDE). For a MDE(s) with an offset date within two months to five years from the time of the study screening visit, medical attention for the MDE is not required. For a MDE(s) with an offset date that is more than five years from the time of the study screening visit, the participant must have received medical attention for at least one of their MDEs. They will be randomized to: (1) tDCS + CR or (2) sham tDCS + sham CR ("sham + sham"). Participants will be followed for 24-84 months or until progression of

those with MCI to dementia (and of those who are cognitively normal to MCI or dementia For the purpose of normalizing the neuropsychological measures, we will also recruit up to 200 controls in order to complete assessments in up to 80 cognitively intact participants age 60 and over.

4.0 Research Design and Methodology

4.1 Methods:

A) Screening, Clinical and Baseline Assessments –

Participants will fall into one of three Groups:

Group 1: "Pure Depression": Group 1 is made up of individuals who have a MDD and do not have MCI, defined as meeting the criteria of either (a) or (b):

(a) Meeting the DSM 5 criteria for one or more MDE(s), with an off-set of 2 months to 5 years from the screening visit date. It is not necessary for this (these) episode(s) to have received medical attention.

(b) Meeting the DSM 5 criteria for one or more MDE(s), with an off-set of ≥5 years from the screening visit date. It is necessary that at least one MDE received medical attention (e.g., previously been on one or more antidepressant(s), saw a psychiatrist, primary care physician, or had a previous hospitalization) and the MDE must have occurred during the individual's adult life (i.e., 18 years of age or older).

Group 2: "Pure MCI": Group 2 is made up of individuals who only have a diagnosis of MCI and no history of depression. In other words, they meet DSM 5 criteria for a MCI diagnosis and do not meet SCID/DSM 5 criteria for a MDE at any time in their adult life.

Group 3: "MCI and Depression": Group 3 is made up of individuals who have a current MCI diagnosis and a MDD. In other words, they meet both DSM 5 criteria for MCI and SCID/DSM 5 criteria both forone or more MDE(s) at any time during their adult life (18 years of age or older) and may or may not have involved the use of antidepressants.

After the risks and benefits of participating in the study are explained to them by a physician, potential participants will be asked to sign an informed consent form. They will then complete the baseline research assessment. Participants will be screened with the Structured Clinical Interview for DSM-IV updated for DSM[127] and with DSM 5 criteria for a mild neurocognitive disorder (MCI) and major neurocognitive disorder ("dementia") to determine eligibility based on inclusion and exclusion criteria.

At the time of enrolment, all participants will have a medical history to assess their physical health, determine whether they can safely participate in the study, and determine whether there might be a medical illness that may be causing some cognitive impairment or other symptoms. In addition, all participants will have had a physical examination and standard laboratory tests within the past 6 months. During screening, if a clinically significant and/or unexpected disease or condition is detected, the individual will be encouraged to follow-up with their primary care physician or report to an emergency room.

Diagnoses of Mild Neurocognitive Disorder and dementia and their subtypes will be based on the updated DSM-5 criteria and will be made during consensus. We will use a comprehensive neuropsychological battery

(see appendix A) that are standardized, reliable, and sensitive to neurological and psychiatric disorders, in particular LLD.

B) **Randomization and Intervention -** To ensure similar populations in the two arms of the study, randomization will be stratified based on having: (1) "Pure MCI" vs. "MCI and Depression", vs. "Pure Depression". Participants in each of these three groups will be randomized to receive either tDCS + CR or sham tDCS + sham CR ("sham + sham").

Cognitive Remediation (CR) - Sessions will be administered in a group setting under the supervision of trained interventionists. Each group will meet daily for 2 hours, 5 days/week, for 8 weeks initially ("induction phase") and then for 5 days every 6 months ("consolidation phase"). In addition, participants will perform CR exercises online at home. Participants will be followed for 24-84 months or until progression of those with MCI to dementia (and of those who are cognitively normal to MCI or dementia). CR group sessions will utilize didactic and drill-based exercises. The computerized drill-based exercises focus on practice and repetition of neurocognitive ability areas that are affected in depression such as attention, processing speed, executive function, verbal memory, and working memory. Performance feedback is given to reinforce progress and the exercises are designed to be enjoyable to complete, with titrated difficulty levels over time. "Strategic monitoring" promotes transfer of cognitive gains to everyday. Participants are also encouraged to discuss how to generalize therapeutic gains in the laboratory to community environments ("bridging").

During home-based online CR, participants will practice drill-based exercises that complement those performed in group sessions and also target attentional control, executive function, working memory, and information processing speed with tasks that adapt within- and between-sessions. Participants will receive training on the use of the home-based exercises. A manual will be provided and a help 1-800 number will be given for assistance in logging into or using the program. Participants will be asked to complete exercises in two 20-minute intervals each day. Online participation will be monitored as participants will have their own accounts. E-mails or phone reminders can be used for participants who do not complete prescribed tasks regularly. Based on previous performance, task difficulty is modified to maintain an optimal level of performance by adjusting the speed, complexity and integrity of target stimuli and the presence and salience of distracter items. Thus, tasks remain challenging enough to produce plasticity but not counterproductively discouraging.

Sham CR - A key feature distinguishing active CR from sham CR is dynamic titration of difficulty. In sham CR, participants are exposed to the same exercises but the difficulty is set at a relatively easy level without adjustment. Sham CR was designed this way because an optimal sham CR should control for cognitive activation without leading to incremental learning.

Transcranial Direct Current Stimulation (tDCS) - tDCS will be administered for 30 min/day, just before the start of each group session. tDCS montage will be bifrontal[91] with one large anode placed over Fz and the cathode over Iz. The direct current will be of 2 mA (current density = 0.57 A/m^2).

Sham tDCS - For sham tDCS, the device will be turned off after 1 min of active stimulation. In other studies[92,93], this approach has ensured that the participants are blind to the type of stimulation (active vs. sham) since the mild scratching experienced immediately after initiation of stimulation continue to occur. tDCS and sham tDCS will be administered by trained interventionists to ensure that its administration remains standardized throughout the study.

C) **Frequency of Assessments**

All participants will be thoroughly assessed (pre-screened) as part of good clinical care by their clinician outside of the study and before starting the study.

Baseline (T0): Confirmation of eligibility and baseline assessment (including mood, cognition, function, and biomarkers). This assessment will be split over several days to reduce participant burden. Following consent, the participant will be randomized to either tDCS + CR or sham tDCS + sham CR in the database. After the baseline assessments and randomization are completed participants will start an 8-week course of tDCS + CR or sham + sham and every 6 months one-week consolidation sessions and also complete on-site assessments every 12 months (for up to 84 months) or until progression of those with MCI to dementia (and of those who are cognitively normal to MCI or dementia).

Follow-Up Assessments: *Measures relevant to cognitive function and mood will be collected at the following time points:*

T2: Following completion of the 8-week induction phase (to assess the short-term effects of tDCS + CR); T3-T9/Tx: every 12 months from T1 or at time of termination (Tx).

In-person booster sessions during the COVID-19 pandemic will occur in accordance to Infection, Prevention, and Control Department's recommendations where the following steps will be followed for every group session:

- Participants will be seated 6ft or more apart from one another. To mitigate risks, everyone will have to undergo CAMH/ Sunnybrook screening procedures at each visit and participants will be required to perform hand hygiene prior to entering the room where the sessions are held.
- The RA will be required to wear a mask and a face shield or goggles when applying the tDCS cap placement where the 6ft physical distancing will not be feasible. Participants will also be wearing masks throughout the booster sessions. Disposable nitrile gloves will also be available for use.
- The tDCS equipment will be wiped down with disinfectant wipes prior to and after each use
- Hand hygiene will be performed before/after each tDCS session and before/after handling tDCS equipment

Induction phase (after randomization/T1) tDCS + CR vs. sham tDCS + sham CR

- tDCS (30 min/day) + CR (2 hours daily)
- 5 days/week, for 8 weeks

Consolidation phase (every six months ± 3 weeks from T1)

tDCS + CR vs. sham tDCS + sham-CR

- tDCS (30 min/day) + CR (2 hours daily)
- 5 days/week, for 1 week

Remote Booster Sessions

The method of administration for boosters will be determined by the participant's preference or by other extraneous factors (e.g., pandemic restrictions).

For those group of participants that are cannot attend the in-person booster sessions (every 6 months), there will be an option to complete the sessions via WebEx at CAMH and via Zoom at Sunnybrook. The video sessions may be recorded for fidelity purposes, the same way it is done during the in-person group sessions. The tDCS administration cannot be done remotely and hence the booster sessions will only consist of the CR exercises. The

WebEx and Zoom sessions will be securely transferred from the researchers' CAMH WebEx and Sunnybrook Zoom accounts to the study-specific folder on the secure CAMH and Sunnybrook servers within 30 calendar days, at which point the recordings will be deleted from the WebEx and Zoom servers. The WebEx recordings will be maintained and stored as per policy AR1.6 (Research Record Management and Retention) at CAMH and will similarly follow the appropriate policy at Sunnybrook.

Participants will be invited to WebEx/Zoom group meetings led by a trained interventionist who will facilitate the sessions and will provide support and guidance through the exercises. Each group will meet daily for ~ 1.5 hour, 5 days/week, every 6 months ("consolidation phase"). Performance feedback is given to reinforce progress and the exercises are designed to be enjoyable to complete, with titrated difficulty levels over time. "Strategic monitoring" promotes transfer of cognitive gains to everyday.

When recording testing sessions, only digital recording devices and methods approved by CAMH IT security will be used (i.e., it is encrypted, password protected and meets all CAMH related requirements). Personal recording devices will not be used. The recording device will be securely stored under the control of study research personnel while it contains the recordings. Recordings will be transferred to and stored on secure CAMH servers, and will be deleted from the recording device after review.

D) **Monitoring -** The PI of the study or one of the other study physicians will be available: (1) to assist the screening clinician with further evaluation of detected diseases/conditions and assuring that appropriate referrals for safe follow-up care are provided to the individual if needed; (2) during the study to assist with the management of a person deemed to be suicidal.

Antidepressant Clinic Visits and Open Antidepressant Protocol

Participants with MDD will be recruited if they are currently in remission. Participants receiving antidepressant maintenance will be seen regularly by their treating physicians or a psychiatrist associated with the study. Consistent with an intent-to-treat (ITT) approach, relapse or recurrence will be treated following a stepped–care protocol (e.g., maximization of current antidepressant dose or initiation of sertraline, followed by a switch from sertraline to venlafaxine or from venlafaxine to bupropion). Consistent with an intent-to- treat (ITT) approach, once randomized, participants will be kept in the study even if they suffer a relapse or recurrence.

E) **Early Termination from Protocol Treatment-** Participants who progress from MCI to dementia or from cognitively normal to MCI or dementia will be terminated from the protocol and will be referred for standard clinical management of MCI or dementia.

F) **Location of Procedures -** Recruitment, screening, and clinical assessments will take place at each of the 5 sites (Centre for Addiction and Mental Health [CAMH] and University Health Network [UHN] located in downtown Toronto; Baycrest Health Centre; St. Michael's Hospital [SMH], and Sunnybrook Health Sciences Centre [SHSC] located uptown. Cognitive assessments, CR and tDCS sessions will take place at two sites: CAMH (located downtown) and SHSC (located uptown). Biomarkers will take place at CAMH. (If participants refuse to complete MRI, LP, and EEG and only agree to biomarker blood draws and genetics, these samples will be collected at CAMH or SBHSC).

G)

4.2 Schedule of assessments:

Instruments and batteries	Baseline	Randomization/ Treatment									
	T0	T1 (Week 0)	T2	T3	T4	T5	T6	T7	T8	T9/TX	Other
Week		Weeks 1-8	Weeks 9-12	Month 12	Month 24	Month 36	Month 48	~Month 60	~Month 72	~Month 84	
Structured Clinical Interview for DSM Disorders (SCID) (for depression and alcohol eligibility)	•										
Socio-Demographic Information	•										
Montgomery-Asberg Depression Rating Scale (MADRS)	•		•	•	•	•	•	•	•	•	•
NPI-Q	•		•	•	•	•	•	•	•	•	•
Beck Scale for Suicidal Ideation (SSI)	•	•	•	•	•	•	•	•	•	•	•
Modified Hachinski Ischemic Scale	•		•	•	•	•	•	•	•	•	
Handedness Inventory Scale	•										
Driving Questionnaire	•									•	
Medical History	•										
Vital signs – height, weight, blood pressure, pulse rate	•		•	•	•	•	•	•	•	•	•
EKG *(within past 6 months; obtained from health records)* [a]	•										
CIRS-G	•										
PTT, PT INR[b]											•
Smoking Status	•										
E-COG	•		•	•	•	•	•	•	•	•	
Clinical Dementia Rating (CDR)	•		•	•	•	•	•	•	•	•	
Neuropsych. Battery	•		•	•	•	•	•	•	•	•	
EVLT[c]	•		•								
2-item version of PASS	•		•	•	•	•	•	•	•	•	

Instruments and batteries	Baseline	Randomization/ Treatment									
	T0	T1 (Week 0)	T2	T3	T4	T5	T6	T7	T8	T9/TX	Other
Week		Weeks 1-8	Weeks 9-12	Month 12	Month 24	Month 36	Month 48	~Month 60	~Month 72	~Month 84	
Lab test results – (within past 6 months; obtained from health records) Electrolytes, BUN, creatinine, liver function tests, TSH, CBC, folates, B12, HDL-c, TC and others as clinically indicated)	•										
LP[d]											•
EEG[e]	•		•	•	•	•	•	•	•	•	
Genotyping[f]	•										•
Peripheral biomarkers (BDNF) [g]	•									•	•
MRI[h]	•		•							•	
UDS[i]	•		•							•	
tDCS + CR or sham tDCS+ sham CR[j]		•		•	•	•	•	•	•	•	
AE/SAE assessment[k]		•	•	•	•	•	•	•	•	•	•

a) If no EKG record is available through participant's health records, the test will be completed at the recruiting site.

b) Participants who consent to the LP will complete the PTT and PT/INR blood tests sometime before their procedure.

c) The EVLT will be administered at both T0 and T2 for participants who consented after March 22, 2016. For participants who consented before March 22, 2016, the EVLT will be completed at their next scheduled NP visit. The EVLT is to be administered at the end of Day 1 of NP testing (this is the preferable option); or, at the end of Day 2 of NP testing.

d) LPs are optional and should only be performed among those patients who provide consent. LPs should be completed prior to the start of T1 visit and after the imaging scans, however, if extenuating circumstances prevent LPs from being completed prior to T1, the LP can be scheduled and completed anytime in the study.

e) EEG is an optional assessment performed only once a study participant provides informed consent to have EEGs performed. EEGs will take place at the time of each cognitive assessment, specifically, during the working memory task, "N-back".

f) Genotyping should be completed prior to the start of T1 visit, however, if extenuating circumstances prevent them from being completed prior to T1, the sample collection can be scheduled and completed anytime in the study.

g) "Other" timepoint for peripheral biomarkers refers to those that for the LP procedures; these are additional biomarkers that will be collected for those who consent to the LP.

h) MRI is an optional assessment performed only once a study participant provides informed consent to have an MRI Performed. The T0 MRI should be completed at T0, prior to T1 (first intervention visit); however if extenuating circumstances prevent it from being completed prior to T1, MRI can be completed during the 8-week intervention. For Healthy Controls, there will only be one MRI at one of their regularly scheduled T-visits (i.e. T0, T2, T3, etc)

i) Urine Drug Screen (UDS) will be obtained only in participants who consent to MRI

j) tDCS + CR or sham tDCS + sham CR every 6 months between visits T2 and T9.

k) AE/SAE collection from the time of consent.

5.1 Assessments and laboratory measures

The following measures will be used to characterize the participants, ensure they meet the inclusion criteria, and assess the outcomes and treatment response during the RCT.

5.2 Screening Assessment:

Structured Clinical Interview for the DSM-V (SCID)- Participants will be screened with the Structured Clinical Interview for the DSM-IV updated for DSM 5 and DSM 5 for MCI, MDE, and Major Neurocognitive Disorder (dementia) to determine eligibility. The SCID assesses current and lifetime depression and other psychiatric disorders. It will be used to clarify psychiatric inclusion and exclusion criteria.

5.3 Assessment of depressive symptoms:

The Montgomery-Asberg Depression Rating Scale (MADRS)[122] will be our main outcome measure. A MADRS score ≤10 at baseline will establish study eligibility. The MADRS was designed to be used by both psychiatrists and non-psychiatrist raters. It is a 10-item checklist. Items are rated on a scale of 0-6 with anchors at 2-point intervals. **The MADRS takes approximately 15 minutes to administer.**

5.4 Dementia scales:

E-COG- This questionnaire is used as a screening tool to evaluate dementia. Higher scores on this scale indicate greater cognitive impairment. **Administration time is approximately 10 to 15 minutes.**

Clinical Dementia Rating Scale (CDR)- This scale is useful in quantifying the severity of dementia based on six domains of cognitive and functional ability: memory, orientation, judgement and problem solving, community affairs, homes and hobbies, and personal care. Each item is rated on a 5-point scale through a semi-structured interview with the participant or reliable informant. **Administration time is approximately 40 minutes.**

5.5 Assessment of functional status:

Performance Assessment of Self-Care Skills (PASS): The 2-items version of PASS (ReCALL), shopping capacity and financial capacity (bill payment and chequebook balancing) are assessed. **It takes approximately 20 minutes to administer.**

5.6 Suicidal ideation:

Suicidal ideation is a key dimension of MDD because of the high suicide rates in depressed elders and because it independently predicts treatment outcomes. A systematic evaluation of suicidal ideation is needed in any depression treatment study for safety reasons and because clinicians need to know the effects of treatment on suicidality to understand risks vs. benefits.

Scale for Suicide Ideation (SSI) - We will use the 21-item Scale for Suicide Ideation (SSI). It has been shown to predict completed suicide[123, 124] and has moderately high internal consistency with Cronbach's alphas ranging from 0.84 to 0.89 and good interrater reliability[125, 126]. To reduce participant burden, five screening items are administered; if any is endorsed, the participant completes items 6-19. Items 20 and 21 assess previous suicide attempts. **The full SSI takes 10 minutes to administer.**

5.7 Neuropsychiatric Inventory Questionnaire (NPI-Q): The NPI-Q is used to measure 12 categories of behavioral disturbance, in particular: Delusions, Hallucinations, Anxiety, Depression/Dysphoria, Agitation/Aggression, Elation/Euphoria, Disinhibition, Irritability/Lability, Apathy/Indifference, Motor Disturbance, Nighttime Behavior Problems, and Problems with Appetite/Eating. The presence of the symptom as well as its severity and frequency over the last month is based on caregiver report. The NPI-Q is widely used in clinical AD trials as a behavioural outcome measure and is included in longitudinal studies such as the Alzheimer's Disease Neuroimaging Initiative (ADNI)[128,129]. The administrator ranks the severity of each behavior exhibited on a scale of 1 to 3, with 3 being the most severe. The total severity score is the sum of the severity scores obtained for each behavioral category. Additionally, the administrator ranks the patient's level of distress from each behavior, on a scale of 1 to 5, with 5 indicating the most severe level of distress. The total distress score is the sum of the distress scores obtained for each behavioral category. **The assessment takes approximately 10 minutes to** administer.

5.8 Driving Questionnaires:
The driving questionnaires included are used to measure: i) how much the participant drives and in what circumstances they drive (Situational Driving Frequency); ii) in what situations the participant avoids driving (Situational Driving Avoidance); iii) the participant's perception of their driving ability (Perceived Driving Ability); iv) their comfort driving in the day or at night (Driving Comfort); and v) the participant's decision-making processes regarding driving (Decision Balance-Plus). **The questionnaires are self-administered at study entry and study termination, and will take 10-20 minutes to complete.** In cases where participant is unable to complete an in-person TX visit, the questionnaire will be administered over the phone with the participant and informant (if necessary).

5.9. Clinical Assessments Administration

All follow-up clinical assessments (MADRS, NPI-Q, SSI, Driving Questionnaire, Medical History, AE/SAE Assessment) can be conducted in person as well as remotely (i.e., via WebEx or telephone). The method of administration will be determined by the participant's preference or by other extraneous factors (e.g., pandemic restrictions). During the COVID-19 pandemic, each participant scheduled for in-person appointments will undergo CAMH and other institutional (i.e., Baycrest, St. Michael's Hospital, Sunnybrook Health Centre, University Health Network), screening procedures prior to their visit and on the day of their visit and wear a surgical mask for the duration of the on-site visit.

5.9 Cognitive assessments:
The proposed battery developed with Meryl Butters, Ph.D. (collaborator at the University of Pittsburgh) is well- established, standardized, reliable, and sensitive to neurological and psychiatric disorders. These instruments draw on many well-validated NP tests to assess cognitive domains of memory, visuo-construction, language, information-processing speed, and executive functioning.

The assessments will be performed by trained psychometrists blind to the interventions. The investigators have published on the importance of achieving high levels of inter-rater reliability in multisite trials and they have developed methods to train and certify psychometrists on various instruments.

Similar to clinical assessments, cognitive assessments can be done in person or remotely (via telephone or using WebEx/Zoom). Telephone calls or assessments done via teleconferencing/videoconferencing using WebEx may be recorded. Some assessments are modified to accommodate the change in format of administration while maintaining the validity and integrity of the data. The assessments that cannot be done via phone or videoconference will not be done (Table 5.9).

Remote Administration of Neuropsychological Assessments

Participants will be mailed large envelopes with an instruction sheet, a sealed envelope, and a pre-paid return envelope inside. The Instruction sheet will ask participants not to open the sealed envelope until they are instructed to do so. The sealed envelope will be opened during the videoconference. It will contain the necessary testing forms. Tasks will be administered via phone or videoconferencing with Screen Sharing (refer to table 5.9 below). When testing is completed, participants will mail back all completed forms and test stimuli using the return envelope provided.

When recording testing sessions, only digital recording devices and methods approved by CAMH IT security will be used (i.e., it is encrypted, password protected and meets all CAMH related requirements). Personal recording devices will not be used. The recording device will be securely stored under the control of study research personnel while it contains the recordings. Recordings will be transferred to and stored on secure CAMH servers, and will be deleted from the recording device after review.

Table 5.9. Neuropsychological Assessments

Administration Methods Legend:
1. In-person
2. Via phone
3. Via WebEx/Zoom
3a. Assessments remaining the same as in-person
3b. Assessments modified to allow for remote administration
4. No available remote methods; assessment will not be administered remotely

Name of Assessment	Administration Method
California Verbal Learning Test (CVLT-II)	1 or 2 or 3a.
Brief Visuospatial Memory Test (BVMT-R)	1 or 3a.
Trail Making A & B	1 or 2* or 3a*
Coding	1 or 2 or 3a. .
Stroop	1 or 2 or 3a.
Judgment of Line Orientation (JLO)	1 or 2 or 3a.
2-item version Performance Assessment of Self-care Skills (PASS)	1 or 3b.

Continuous Performance Task (CPT)	1 or 4.
Clock Drawing	1 or 2 or 3a.
Letter & Semantic Fluency	1 or 2 or 3a.
Boston Naming Test (BNT)	1 or 2 or 3a.
Paced Auditory Addition Test (PASAT)	1 or 4.
N-Back EEG	1 or 4.
N-Back	1 or 3a
Everyday Cognition (E-Cog): Self & Informant	1 or 2 or 3a.

*for participants that do not have access to a computer, only Oral Trail Making A+B will be administered over the phone. For Webex/Zoom sessions, both Oral Trail Making and regular Trail Making will be administered.

5.10 Emotional Verbal Learning Test (EVLT):

The EVLT is an emotional memory test developed as a screening tool for preclinical AD. Participants are read three lists of words and asked to recall as many of these words as possible. Each list contains fifteen common words, five of which are positive, negative and neutral. The test will cause minimal participant fatigue. The EVLT will be administered at both T0 and T2 for participants who consented after March 22, 2016. For participants who consented before March 22, 2016, the EVLT will be completed at their next scheduled NP visit. The EVLT is to be administered at the end of Day 1 of NP testing (this is the preferable option); or, at the end of Day 2 of NP testing. **The test takes approximately five minutes to administer.**

5.11 Biomarkers:

We will collect biomarkers to conduct exploratory analyses on the pro-cognitive neuroplasticity effects of tDCS + CR.

MRI Scan- Acquisition: We will obtain MRI data on the 3 Tesla GE Echospeed (General Electric, Milwaukee, WI) research-dedicated scanner at CAMH. This scanner permits maximum gradient amplitudes of 50 mT/m and is equipped with an eight-channel head coil that provides major improvement in signal to noise ratio (SNR) over the standard quadrature coil[94]. The T1-weighted scan will be acquired as a sagittal 3D FSPGR: (echo time (TE): 3 ms; repetition time (TR): 8.2 ms; time to inversion (TI): 650; flip angle 8, FOV=24 cm; number of excitations (NEX) = 1, with 0.9 mm isotropic voxels, no gap). For DTI, we will use an echo planar imaging (EPI) sequence with dual spin echo option to reduce eddy-current related distortions[95] and ASSET with a SENSE-factor of 2. We will acquire 60 gradient directions with b=1000, 5 baseline scans with b=0. Scan parameters are: TR 8800 ms; TE min; FOV 38 cm; 128x128 encoding steps; 2.0 mm isotropic voxels, no gap. Axial slices will be acquired parallel to the AC-PC line covering the whole brain. B0 field inhomogeneity maps will also be collected and calculated. An exploratory multi-shell diffusion acquisition will also be acquired. For resting state fMRI an oblique/axial will be acquired with TR=2000, TE=30.0, FOV = 20 cm, Flip angle 77, Slice thickness = 4 mm, 40 slices (7 minute run). The entire scan session will take approximately 30 minutes. The entire scan session (including functional neuroimaging described below) will take approximately one hour.

Cortical Thickness Analysis: Following acquisition, all T1-weighted MRI data will be submitted to the

CIVET pipeline (version 1.1.10). T1 images will be registered to the ICBM152 nonlinear sixth generation template with a 9-parameter linear transformation, inhomogeneity corrected[96] and tissue classified[97,98]. Deformable models will then be used to create white and gray matter surfaces for each hemisphere separately, resulting in 4 surfaces of 40,962 vertices each[99, 100]. From these surfaces, the t-link metric will be derived for determining the distance between the white and gray surfaces[101]. Cortical thickness maps will be aligned across all scans using non-linear surface based registration[102, 103]. The thickness data will then be blurred using a 20-mm surface based diffusion blurring kernel[104] in preparation for statistical analyses.

DTI Analysis: All diffusion-weighted scans will be preprocessed using eddy current correction and nonlinear EPI distortion correction, filtering, and tensor estimation (3D slicer software, www.slicer.org). A deterministic whole brain tractography approach[105] and an eigenvector tracking algorithm based on the fourthorder Runge-Kutta method will then be used to track white matter fibers. The linear anisotropy measure (C_L) will be used for seeding and stopping thresholds instead of FA, because it lessens the effect of planar partial-volume regions where a fibre may jump from one structure to another. By reducing partial-volume tractography errors, it improves the ability of the clustering to separate different structures[106]. For segmentation, our clustering method takes advantage of fibre shape and groups fibres of similar appearance. Once the whole brain cluster model is produced, a trained operator combines the clusters that correspond to a fiber tract[107, 108] (e.g. genu of corpus callosum). We have shown excellent reliability of this method in Schizophrenia participants for our white matter tracts of interest[108]. On an exploratory basis we will also measure axial diffusivity (sensitive to axonal membranes), and radial diffusivity (sensitive to myelin)[109] to understand more about the specific tissue compartments that may contribute to potential changes in mean diffusivity .

Resting state fMRI Analysis: Scans will be pre-processed as described in detail in several recent publications[110,111]. Structural images will be spatially registered to a group average anatomical image intended to serve as an unbiased anatomical template. We have employed this template in previous studies[111,112]. Functional data will be slice-time corrected using AFNI (afni.nimh.nih.gov/afni) and head motion corrected using AIR (bishopw.loni.ucla.edu/air5/). For each run, mean functional volume will be registered with each participant's structural volume using a rigid body transformation model. We will then apply the FSL/FNIRT registration algorithm to find a non-linear transform between our template and MNI 152_T1 provided with FSL software (www.fmrib.ox.ac.uk/fsl). Data will be smoothed using an 8 mm Gaussian kernel.

We will correct transformed functional volumes with Independent Component Analysis (ICA) within separate runs, as implemented in FSL/Melodic[113]. We will further adjust voxel time series by regressing out motion correction parameters, white matter, and cerebrospinal fluid time series. To help localize regions from our functional output, we will submit MNI coordinates to the Anatomy Toolbox in SPM8, which applies probabilistic algorithms to determine the cytoarchitectonic labeling of MNI coordinates[114, 115]. We will then use a published template to identify 20 classic independent components in the data, which will be compared between the environmental enrichment groups[116].

Cerebro-spinal fluid (CSF) a-beta 42, phospho-tau, and tau levels: Since we expect that some participants may be willing to have a lumbar puncture (LP), we will collect CSF from participants who consent to have a one-time LP. We will measure a-beta 42, phospho-tau, and tau levels in their CSF. In our own

experience and in the literature, research participants have been able to tolerate LPs well after a discussion through informed consent and listening to any of their concerns[117, 118]. We estimate that about 40% of the participants will consent to have an LP at the time of randomization. Participants who consent to the LP will complete the PT/INR before their procedure.

The LP procedure for this study does not differ from the routine diagnostic LP performed at a neurologist's office: participants are first screened for risk of bleeding complication (they should not be on anti-coagulants and certain anti- platelet agents may be held for the day prior to the procedure) or herniation. Participants will be informed of the potential minimal risks of bleeding and infection and of the risks of post-spinal headache. It is hard to predict which participants will develop the headache. As we have done in other studies, if participants develop a moderate or severe headache that persists beyond a day, we will refer them to a local anaesthesiologist for a blood patch procedure. We will collect up to 15 mL of CSF from each participant, and use 4mL for analysis of a-beta 42, phospho-tau, and tau levels. We will store the remainder

for repeat or further testing, should other relevant CSF biomarkers be identified during the study period.

We will use the CSF samples from this study to assess potential neurological markers associated with aging. The CSF may be shared with study collaborators in order to analyze and assess the samples.

Genotyping: Genetics sampling will take place at CAMH or SHSC. CAMH or SHSC will collect either whole blood preserved in EDTA or saliva, store for the short term, and ship batched samples at regular intervals to Dr. Kennedy's CAMH laboratory. We will request a second specimen from any subject from which DNA is not isolated from the initial collection. Upon receipt of the samples, Dr. Kennedy's lab will extract DNA from the specimens. At this time, we are planning to genotype 32 SNVs from among common variants associated with AD As new SNVs are identified, other approaches to genotyping may be used.The dataset including DNA samples will be available as a resource to researchers for future studies. We will work with the coded sample and will store the sample securely. The lab personnel will be blind as to the status of each sample. That is, the researcher coding the genes will not know the diagnosis of the participant.

Theta-gamma Coupling: We will offer an optional Electroencephalogram (EEG) to study theta-gamma coupling during the working memory task ("N-back") as a probe of the DLPFC function. To measure theta-gamma coupling, EEG will be acquired through a 64-channel Synamps 2 EEG system. An EEG cap will be used to record the cortical signals, and four electrodes will placed on the outer side of each eye, and above and below the left eye to correct for eye movement artefacts in the analysis. Electrodes will be referenced to an electrode posterior to Cz electrode. EEG signals will be recorded using direct current and a low pass filter of 100 Hz at 20 kHz sampling rate[100]. The electrodes that will be used to measure coupling during N-back performance will be the right and left frontal electrodes: AF3/4, F7/8, F3/4, and F1/2.

EEG Data Preprocessing: EEG recordings will be processed offline using MATLAB (The MathWorks Inc. Natick, MA, USA) and EEGLAB toolbox. EEG data will first be segmented with respect to stimulus such that each epoch included 1300 ms pre-stimulus baseline and 3052 ms post-stimulus activity. Epochs will be baseline corrected with respect to the pre-stimulus interval (1000 ms to 10 ms prior to the stimulus) and filtered by using a zero-phase shift 1–120 Hz band pass filter. The 60-Hz power line artifact will be removed from each trial across all channels by using the Thomson F-test based on multitaper spectral estimate

techniques. We will then create an channels-by-trials matrix of 1 s, and alter the value to zero if an epoch has: (1) amplitudes larger than +/- 150 μV, (2) power spectrum that violates 1/f power law, (3) standard deviation that is 3 times larger than average of whole trials, (4) kurtosis that is 3 times larger than average of whole trials, or (4) skewness that is 3 times larger than average of whole trials. Then, we will first reject channel(s) if its corresponding row represents zeros in more than 55% of trials. Second, we will remove epoch(s) if a trial has zeros in more than 20% of channels. Then, an independent component analysis (EEGLAB toolbox; Infomax algorithm) will be performed to remove eye-blink traces, muscle artifacts and/or head movements from the EEG data. Finally, an average signal will be obtained from each electrode for each subject. For more details, please see our recently published paper using these methods (Rajji et al. 2013)[130].

Theta Phase-Gamma Amplitude Coupling: We will measure theta-gamma coupling as a relationship between the phase of theta (4-7 Hz) and the amplitude of gamma (30-50 Hz) as we have recently reported using another form of brain stimulation[130]. We will perform the analysis on the time averaged file of each subject using Matlab by adapting previously published methods[131,132]. We will first filter the signal into separate theta and gamma waveforms with a zero-phase shift filter and then applied the Hilbert transform. Using the phase information of the theta wave, we will sort the corresponding gamma amplitudes into 6 bins (i.e. -180° to -120°, -120° to -60°, -60° to 0°, 0° to 60°, 60° to 120°, 120° to 180°) and then average them. Since the angle values correspond to a cosine reference, zero degrees correspond to a peak of the waveform. In order to quantify coupling, we will use an entropy based modulation index (MI)[132]: **MI = [(log(*N*) – H(P)] / log(*N*).** *N is* the number of phase bins, log(*N*) represents the entropy of a uniform distribution, *P* is the relative amplitude distribution sorted according to phase bins, and *H(P)* is the entropy of the *P* distribution, which is calculated as:

$$\mathbf{H(P)} = -\sum_{\mathbf{j=1}}^{\mathbf{N}} \mathbf{P(j)}\log[\mathbf{P(j)}]$$

We will calculate the relative amplitude distribution P for each subject by dividing the amplitude of each phase by the sum of all amplitudes across bins. This maximum entropy for such a relative amplitude distribution happens when the amplitude is 1/N, which occurs when the distribution is uniform. Since an increase in coupling represents an increase of order, higher coupling translates to lower entropy H(P), which in turn results in a high MI value. We will generate surrogate data for each subject by maintaining the amplitude spectrum while randomizing the phase[131]. A total of 200 iterations will be done in order to generate an empirical distribution under the null hypothesis of no coupling.

Peripheral Biomarkers: At this time, we are planning to measure brain derived neurotrophic factor (BDNF) due to its noted relationship with plasticity and cognitive performance. However, other biomarkers relevant to brain plasticity and cognitive reserve may also be characterized.

6.1 Data analysis and Management

6.2 Power Analysis:

The power analysis assume a two-tailed α value of 0.05, 125 participants in each group and are based on the donepezil prevention trial[8] in which participants with LDD had a global cognition z-score (compared to healthy controls) of about -0.50 (SD=0.80) after they responded to an antidepressant and a yearly decline of -0.40 on

placebo. For H1, we will have adequate power of 84% at α of 0.05 to detect a difference between the two groups if the yearly decline in z-score in the tDCS + CR group is reduced to -0.10. For H2, hypothesizing that tDCS + CR halves the monthly progression rates (from 1.37% to 0.68% overall), we will have adequate power of 80% at α of 0.05 to detect this hazard ratio (HR) of 0.50. For H3, we will have adequate power of 85% at α of 0.05 if z-scores acutely improve by 0.30 with CR+tDCS (corresponding to a Cohen effect size of 0.38).

6.2 Data Management and Analysis:

At the time of the study start, the Applied Health Research Centre (AHRC) in the Li Ka Shing Knowledge Institute of St. Michael's Hospital oversaw the daily operations of the data coordination; wrote the data entry guidelines and the data management plan, maintained the central study files, and lead development of the electronic Case Record Form (eCRF) and the research database, configure user accesses within the database. The AHRC will write custom reports and will make periodic updates to the database as necessary. They were responsible for reviewing entered data; raising, reviewing and closing system and site queries; creating customized reports for both reporting (e.g., analyses and reports for DSMB) and data validation purposes.

During the study, the data from this study was transitioned into secure databases maintained by the CAMH Neuroinformatics, including REDCap, XNAT and LabKey. The database structure and management principles will remain the same as the original database with AHRC. At point-of-entry, data values will undergo consistency edits (e.g. ID validation, range verification, duplicate detection) and personnel will be required to correct errors. Reports will be created via the REDCap program. Data management staff at CAMH will run logic error programs to check for accuracy and irregularities within and across data structures and within and across sites. Quality assurance checks will be conducted regularly by site personnel, as well as by CAMH data management staff. Weekly/ Monthly reports will be generated (as needed) to monitor site data timeliness, completeness, and accuracy as well as participant flow through the study. Although unlikely, instances may occur where the databases are not available. In the case that this happens, we will follow the CAMH downtime procedures.

Following the ITT principle, all randomized participants and all available longitudinal data (T0-T9/TX) will be considered in the analyses. We will account for missing data with terminations as being due either to study design (e.g., progression to dementia) or to any other type of termination (for example, adverse events). We will compare the temporal patterns of termination status by treatment arm for each type of termination by examining cumulative incidence curves adjusted for the competing causes of termination[119]. We will account for the impact of non- ignorable missing data through appropriate statistical modeling[120].

For H1 (and H3), we will first use an ANCOVA to test changes in cognition scores with age, education, and depression measure as covariates. We will also use a repeated measures mixed-effects ANCOVA, which is superior to standard ANCOVA in handling missing data. These mixed-models with longitudinal data controlling for age, years of education, and scores at randomization (T1) will be used to compare cognitive and functional performance in the two groups over time. Covariates such as ApoE allele or family history of dementia can be used as moderators. If the depression recurrence rates are different in the two groups, the analysis can use the Ham-D scores as time-varying covariates. ITT differences in slopes of change across time in cognitive and functional performances between the two groups will be tested and estimated using likelihood ratio testing. Finally, comparisons of the two groups with respect to time to pre-specified decreases in scores will be performed with discrete time survival models. For H2, we will use Kaplan-Meier curves to quantify the percentage of those who remain free of MCI or dementia over time. Cox proportional hazard models will be used to quantify hazard ratios comparing the two treatment groups. Tests of proportionality will be conducted following Grambsch and Therneau[121], after checking that proportionality assumptions are valid. Formal tests of treatment x MCI interaction and treatment effectiveness for those with normal cognition or MCI at baseline will use Cox proportional hazard models.

In addition, we will address questions related to the relationship of clinical variables and biomarkers. To perform these analyses, we will use appropriate analytical methods building on the strengths of the investigators.

7.0 e-CRF Entry

The eCRFs will be built with customized edit checks to detect non-conformant data, missing data, and inconsistent data (for example: blank fields, future dates, dates inconsistent with study time frame, data value outside of expected range) and immediately flag these to the attention of the user entering data. These checks assure that common data entry errors are not made. There is also an audit trail, indicating the user responsible for the entry and a time stamp to allow for feedback as required.

Data will be entered into the eCRF either manually or electronically. Direct Entry of Data Into the eCRF (real time) many data elements (e.g., blood pressure, weight, resolution of a symptom or sign, clinical assessments, social – functional tasks) will be obtained at a study visit and will be entered directly (real time) into the eCRF by an authorized data originator. This direct entry of data will eliminate errors by not using a paper transcription step before entry into the eCRF. The eCRF will include the capability to record who entered or generated the data and when it was entered or generated. Changes to the data will not obscure the original entry, and will record who made the change, when, and why and the date and time the data element was entered into the eCRF (the audit trail begins at the time the data are transmitted to the eCRF).Only delegated clinical study staff will perform modifications or corrections to eCRF data. Modified or corrected data elements will have data element identifiers that reflect the date, time, originator and reason for the change, and will not obscure previous entries. Prompts will be designed to alert the data originator to missing data, inconsistencies, inadmissible values (e.g., date out of range), and to request additional data where appropriate.

Authorized personnel (e.g., REB auditors, other monitors) can view the data elements in the eCRF before and after the investigator has electronically signed the completed eCRF. A list of the individuals with authorized access to the eCRF will be maintained. All authorized personnel will have documented training and be assigned their own identification (log-on) codes and passwords. Log on access will be disabled if an individual discontinues their involvement in the study.

8.0 Human Participants

We plan to recruit up to 500 participants in order to enroll 375 in the following groups:
1) Participants with a diagnosis of Mild Neurocognitive Disorder with no history of depression (pure 'MCI')
2) Participants with diagnosis of MDD, Single or Recurrent, in Remission

In addition, we plan to recruit up to 200 healthy control participants in order to enroll up to 80 non-demented, non-depressed healthy controls that also match the age groups of the cases (MCI, MDD) enrolled in the study.

8.1 Inclusion/Exclusion Criteria:
No exclusion criteria are based on race, ethnicity, gender, or HIV status.

To be admitted to this study, participants must satisfy the following inclusion and exclusion criteria:

MCI Group

Inclusion:

- Age ≥ 60 (on day of randomization)
- DSM 5 criteria for Mild Neurocognitive Disorder ("MCI")
- Willingness to provide informed consent
- MADRS score of 10 or below
- Availability of a study partner who has regular contact with the participant
- Ability to read and communicate in English (with corrected vision and hearing, if needed)

Exclusion:

- Met DSM 5 criteria for Major Depressive Episode in past 10 years.
- Lifetime DSM 5 diagnosis of schizophrenia, bipolar disorder, or OCD.
- DSM 5 diagnosis of alcohol or other substances use disorder within the past 12 months.
- High risk for suicide.
- Significant neurological condition (e.g., stroke, seizure disorder, MS)
- Unstable medical illness, (e.g., uncontrolled diabetes mellitus or hypertension)
- Having taken a cognitive enhancer (acetylcholinesterase inhibitor or memantine) within the past 6 weeks.
- Participants taking anticonvulsants, and other psychotropic medication (see exceptions below) that cannot be safely tapered and discontinued. The following psychotropic medications are allowed: i) any antidepressant; ii) zopiclone, trazadone, or a benzodiazepine if they have been taken at a stable dose for at least 4 weeks prior to study entry and; iii) gabapentin and pregabalin if they have been
- taken at a stable dose for at least 4 weeks prior to study entry AND if prescribed for chronic pain.
- A pace-maker or other metal implants that would preclude safe use of tDCS.

MDD Group

Inclusion:

- Age ≥ 65 (on day of randomization)
- Meets DSM 5 criteria for one or more MDE(s)with:
  a) an offset of 2 months to 5 years from the screening visit date. It is not necessary for this (these) episode(s) to have received medical attention *OR*
  b) an offset of 5 years or more from the screening visit date. It is necessary that at least one MDE received medical attention (e.g., previously been on one or more antidepressant(s), saw a psychiatrist, primary care physician, or had a previous hospitalization). Also, the MDE must have occurred during the participant's adult life (i.e., at 18 years of age or older).
- MADRS score of 10 or below
- Willingness to provide informed consent
- Availability of a study partner who has regular contact with the participant
- Ability to read and communicate in English (with corrected vision and hearing, if needed)

Exclusion:

- Meets DSM 5 criteria for Major Neurocognitive Disorder ("dementia")
- Lifetime DSM 5 diagnosis of schizophrenia, bipolar disorder, or OCD
- DSM 5 diagnosis of alcohol or other substances use disorder within the past 12 months.
- High risk for suicide.

- Significant neurological condition (e.g., stroke, seizure disorder, MS)
- Unstable medical illness (e.g., uncontrolled diabetes mellitus or hypertension)
- Participants taking anticonvulsants, and other psychotropic medication (see exception below) that cannot be safely tapered and discontinued. In addition to any antidepressant, the following psychotropic medications are allowed if they have been taken at a stable dose for at least 4 weeks prior to study entry: zopiclone, trazodone, or a benzodiazepine; and gabapentin or pregabalin if prescribed for chronic pain.
- Having taken a cognitive enhancer (acetylcholinesterase inhibitor or memantine) within the past 6 weeks.
- A pace-maker or other metal implants that would preclude safe use of tDCS.
- Received electroconvulsive therapy (ECT) within 6 months of baseline neuropsychological testing.

Control group

Inclusion:

- Age $\geq$ 60
- MADRS score of 10 or below
- Willingness to provide informed consent
- Ability to read and communicate in English (with corrected vision and hearing, if needed)

Exclusion:

- Meets DSM 5 criteria for Minor or Major Neurocognitive Disorder
- Any other lifetime DSM 5 diagnosis except for simple/specific phobias
- Significant neurological condition (e.g., stroke, seizure disorder, MS)
- Unstable medical illness, (e.g., uncontrolled diabetes mellitus or hypertension)
- Participants taking anticonvulsants, and other psychotropic medication (see exception below) that cannot be safely tapered and discontinued. The following psychotropic medications are allowed if they have been taken at a stable dose for at least 4 weeks: zopiclone up to 15 mg/day; trazadone up to 150 mg/day; benzodiazepine at a dose of up to 3 mg/day lorazepam-equivalents; gabapentin and pregabalin (if prescribed for pain).
- A pace-maker or other metal implants
- Neuropsychological testing within the past 12 months

We plan to work collaboratively with the participant's personal physician. All participants will complete a thorough evaluation of their physical health. If the psychiatrist or PCP of a potential participant thinks in his or her professional judgment that the participant cannot or should not participate in the study the participant will not be enrolled.

9.0 Recruitment Procedures

The five sites (CAMH, St. Michael's Hospital, and UHN located in downtown Toronto; Baycrest Health Centre and SHSC located uptown), have busy geriatric psychiatry clinics where, collectively, more than 3,535 older new patients are assessed yearly, with 1,210 new referrals for assessment and treatment of depression in the absence of a dementia.

Recruitment for this study will be conducted through a few different methods:

1) The process can be initiated by the clinical team who is treating the potential study participant. The treating physician/clinical care team will not obtain consent. They may identify potential research

participants and obtain verbal permission from these potential participants for a member of the research team to approach them. Potential participants who indicate a further interest in hearing more about the study and provide assent to be contacted by a member of the research team will then be contacted by a member of the research team who will engage them in a pre-screen process which can be completed over the phone. The potential participant will then be invited to attend an appointment to review the informed consent.

The study can be advertised through various sources (e.g. the newspaper, magazines, radio, etc.) and/or study flyers can be posted in the community. The research registry at each of the five sites (CAMH, St. Michael's Hospital, UHN, Baycrest Health Centre and SHSC) is an online source of advertising that we will also utilize to post our study. We will also utilize online social media advertising (e.g. facebook, twitter) in order to promote our study using the REB approved flyers. Potential participants (including healthy controls) who express interest in the study by responding to the advertised contact information/research registries will complete the pre-screen questions with the RA over the phone. All pre-screen results are discussed with the site investigator(s) in order to establish the best type of clinical assessment/appointments for determining their potential fit for our research study. Potential participants are then contacted by the RA to explain the next step in booking a clinical appointment which will be covered by OHIP and is not considered a part of the study visit. This initial clinical appointment is used to help determine whether the potential participant will be a good candidate for our study. Potential participants are reminded that they will not be compensated for this clinical appointment as it is just a clinical assessment. If the clinical team determines the patient to be a good candidate for the study, the RA will then invite the potential participant to attend an appointment to review the informed consent.

2) Other recruitment strategies will involve referrals by word of mouth and referrals by clinicians and community presentations to lay groups of elderly and their families. We will also contact former research participants who previously consented to be contacted for future research studies from the Geriatric Mental Health Services at CAMH. To avoid cold calling, the participants will be contacted by someone the former participant knows such as the participant's former research coordinator. The procedures outlined above (see #2) will be followed in order to determine the eligibility of each referral/potential participant who expresses interest in our study.

Primary care screening will depend on the various partnerships with several primary care or other health networks. We will accept clinician referrals from these practices and will also use affiliations with community agencies. In case of referrals from other programs, the treating physician/clinical care team will first identify potential research participants. The physician/clinical care team will inform the participants discuss the research project with the participant. If he/she expresses interest in study participation, he/she will be asked to give verbal consent to the physician/clinical care team for a member of the research team to approach them with information regarding participation in the research protocol. Protected health information of potential participants from other programs will be accessed only after written consent has been obtained from the participant.

The participant's recorded contact information will be stored by the researchers in a secure manner (e.g., locked offices, password protected database) accessible only to the researcher who was provided this information and other members of the research team involved in the conduct of the research study for which this information was originally provided. The participant's recorded contact information will be destroyed immediately after researchers have contacted the participant to discuss the research study for which this information was originally provided or after ascertaining that the participant is not eligible for or declines

participation in the research study.

Capacity to provide consent will be assessed on an individual basis. Potential participants will have their capacity assessed by one of the study investigators or another study psychiatrist on the research and a note documenting the results of this assessment will be entered into the participant's medical and research records.

Even after a patient has provided initial consent to participate, we will use subsequent visits, and the implementation of study procedures as opportunities to again explain what is being done and to assure continuing informed consent.

Study staff will review the study procedures, risks, benefits, and all other pertinent information contained in the consent form. The purpose of the research study, the procedures involved in the conduct of the study, potential risks and benefits, and the rights of study participants will be discussed with the potential participant prior to the attainment of written informed consent. Questions will be asked of participants to ensure they understand the nature of the research, the risks and potential benefits of participation, and their rights as research participants. We believe that consent is an ongoing process in any study, and we will continue to educate participants about the nature of the research and address any questions that may arise throughout the course of the study. We are not planning proxy consent.

10.0 Consent Procedures

Voluntary informed consent is required for participation in this study. No study procedures will be undertaken until such consent is obtained from participants. Consent will be documented on a written Informed Consent Form (ICF) or on an Informed Consent Update Form. Full explanation about the study and any applicable updates will be provided to the participants whenever there are any protocol changes. Consent will always be obtained by appropriately trained and qualified study research personnel who do not have an existing clinical relationship with the participant. The study PIs will not obtain participant consent. Even after a participant provides initial consent to participate, baseline as well as subsequent visits/ phone calls, will be used as opportunities to again explain the study details to assure informed consent on the part of participants. The process of obtaining consent will be documented in every case. Documentation of the consent discussion will be entered into the participant's research records (i.e, consent date, version #, and consent choices). Further, the signed consent form will be uploaded into participant's medical records as this study is a treatment clinical trial.
REDcap and Informed Consent Checklist will also be used to document the consent process, including the consent method, date, version, and the consent decisions and options applicable to each version.
Research procedures will only begin once consent documentation has been completed in accordance with the outlined procedures.

There are a few different ways informed consent can be obtained from participants in the study. The mode of collecting consent will be documented in each participant's research record on the study's database.

1) Verbal Consent:

   Verbal consent definition: *A consent process whereby the consent discussion is conducted remotely, the participant confirms their consent verbally, and the consent documentation is completed by the study team (i.e., the ICF is not signed by the participant).*
   Participants will be verbally informed of changes/ updates to the study via telephone and informed consent will be obtained for ongoing participation. The informed consent document will be shared with the

participants prior to the consent discussion so they can follow the document during the phone discussion. The RA will either email or mail the consent document as per the participant's preference.

Informed consent will be obtained using the REB-approved consent script and it will be printed out and signed by the RA obtaining the consent from the participant and a witness observing the consent discussion. The witness will not be the principal investigator/project lead, an individual with a clinical relationship to the participant, a research volunteer, or the person conducting the consent discussion. The witness will be an observer to the consent discussion (i.e., they are not part of/do not contribute to the actual discussion) and will be able to hear both the person conducting the consent discussion and the participant. Wet-ink signatures (from RA obtaining consent and witness) will be obtained according to each institution's guidelines.

A copy of the signed ICF will be provided to the participant via mail and/or email, in accordance with the participant's wishes. The original copy of the signed ICF will be filed in the Informed Consent binder (separate from the participant's research records). The Informed consent process will be documented using the study's database on REDcap by filling out a form that will indicate the consent version, date, consent options and choices, as well as the person obtaining consent.

2) 2) REDcap e-Consent:

Participants can also provide consent using REDCap. RED-cap e-Consent will be used only at those institutions that approve of the process and as per each institution's guidelines.

Participants will be provided with a read-only copy of the ICF via REDCap prior to conducting the consent discussion. The link may be used by participants as many times as they wish (it is not single-use). Upon clicking the link, participants will review the landing page, and continue on to the ICF text. The entire contents of the ICF will be displayed according to the current REB approved consent form, minus the signature/attestation page(s).

Informed consent will be documented using the REDCap e-Consent Framework. Following the consent discussion, the participant will be sent a link to the e-consent via email. The participant will complete the e-consent and be provided with the option to download and/or email themselves the signed ICF.

Following the participant signature, the person conducting the consent discussion will complete the Person Conducting Consent Discussion Attestation Page. PDF copies of the signed ICFs and Attestation pages will be retained in the REDCap File Repository. The research team will provide the participant with a copy of the fully signed ICF via mail and/or email, in accordance with the participant's wishes.

CAMH as the sponsor site will have access to participant names on the electronic consent forms (on the CAMH REDcap database) All other participating sites will not have access to participant information/e-consent forms from the other institutions (i.e. UHN would not have access to CAMH e-consents, for example).

3) Written Paper Consent:

The consents can occur through tele/videoconferencing or in-person. Prior to the consent discussion, Research study staff will provide the prospective participant with the REB-approved ICF, to assist in the consent discussion. This provides the prospective participant time to review the material in advance and/or to follow along during the consent discussion. The research team will use the REB-approved Initial Contact Script to initiate the discussion. Based on the prospective participant's preference and prior agreement, the ICF can be shared via email, mail, courier, or secure file transfer (SFT). If emailed, participants will be given the option to receive a password protected ICF. If mailing the ICF to the prospective participant, the research team will either follow-up with the participant approximately one week after mailing out the ICF, or have the participant contact them (via email or phone) to let them know that they received the ICF.

Regardless of the participant's preferred method of receiving the ICF document, a printed copy will also be mailed to them as the original signed copy will always need to be mailed back to the research team. A prepaid postage envelope will be provided along with a printed copy of the consent and participants will be asked to mail the signed copy back to the team using the prepaid envelop at their earliest convenience.
Once the virtually emailed or mailed ICF is received by the potential participant, the research team will book a scheduled time to go over the consent. The prospective participant must agree in advance to the use of email or institutionally-approved teleconferencing/videoconferencing service (this will be documented using the Initial Contact Script). As always, prospective participants will be provided with as much time as they need to review the consent form, prior to providing informed consent. Research teams will address any questions raised by prospective participants prior to documenting informed consent and make a note of the questions on the Informed Consent Process Checklist. If the participant asks a question that cannot be answered at that time, a separate session should be arranged.

Following the consent discussion, the participant and the person conducting the consent discussion will each personally sign and date the ICF. This process can be conducted in-person or it will be initiated via sending the ICF to the participant via mail, email or Secure Fie Transfer (SFT). The participant will sign the ICF, and the participant will either mail, email (or SFT), fax, the copy or scan/ send photograph of the consent copy back to the study personnel. Once the copy of the signed consent has been received, research procedures will begin but the data obtained will not be used until the original copy of the signed consent has been obtained from the participant. The person conducting the consent discussion will also sign the ICF once received and will send a copy to the participant via their preferred method (e.g., mail, email SFT).

In-person consent can be obtained by meeting with the participant to review the REB-approved consent script. No study procedures will be undertaken until this in-person visit has occurred and consent is obtained and documented from the participant. A copy of the signed ICF will be provided to the participant during that same visit. The original copy of the signed ICF will be filed in the Informed Consent binder (separate from the participant's research records). The Informed consent process will be documented using the study's database on REDcap by filling out a form that will indicate the consent version, date, consent options and choices, as well as the person obtaining consent.

Following Informed Consent:
The participant will receive a fully signed, complete copy of the ICF in a timely manner. A complete copy is all pages of the ICF, including the completed signature page(s).
This may be distributed by mail or email (according to the method the participant agreed to). Alternately, if consent is documented via e-signature software or e-consent platform, this distribution will occur via this technology where this function is supported.

Research procedures may begin once the consent documentation has been completed in accordance with the processes described above.

11.0 Risk/Benefit Ratio

11.1 Risks:

Venipuncture blood draw: Risks of venipuncture blood draws may include mild discomfort and bruising at the venipuncture site and a chance of bleeding, fainting, and/or infection.

Assessments: Assessments may impose some risk emotional discomfort and possible fatigue.

Suicide Risks: When treating depression there is risk that participants attempt or complete suicide. Procedures to manage and mitigate this risk have been carefully thought through; they include close monitoring and termination of participants who deteriorate and require hospitalization.

tDCS: tDCS has previously been used in multiple studies involving older, frail participants with neuropsychiatric disorders such as AD, depression, Parkinson's disease, or stroke, with no adverse sequelae noted. In our own experience, the procedure produces a mild tingling sensation initially which usually completely resolves within 30 seconds. In a study that systematically elicited side effects in 77 healthy controls and 25 participants who underwent 567 tDCS sessions, participants reported a mild tingling sensation (71%), moderate fatigue (35%,), a slight itching sensation under the stimulation electrodes (30%), a mild headache (12%), nausea (3%), or insomnia (1%); only 18% as mildly unpleasant.

Some individuals may experience mild headache or shoulder stiffness after testing, however, these symptoms usually dissipate within 24 hours. Acetaminophen (Tylenol) is effective in treating these side effects.

It should also be noted that there may be side effects and discomforts that are not yet known. Participants will be closely monitored for any adverse effects at each study visit and also on as needed basis.

MRI: Minimal risk except for people with metal or magnetic implants (such as metallic clips in the brain or cardiac pacemakers) due to strong magnetic field in scanner. Participants will be screened by the study personnel and by personnel at the MR center prior to scanning. If an X-ray is required to rule out the presence of metallic fragments, the maximum dose to the involved body area will be 0.3 rems with minimal exposure to other body areas. Also, potential risks to pregnant women are not well-known (but pregnant women are excluded from this study). Some types of (home-made) tattoos can also heat up and cause discomfort.
Individuals with implanted metallic foreign bodies are excluded because the strong magnetic field in the scanner could cause these bodies to change position, injuring participants. In order to assure that MRI scanning is safe to undergo, Metal objects can also become projectile when placed near the magnetic field. This has been reported on a few occasions, but it is a very rare occurrence. Protection from magnetic objects can be safeguarded by the usual safety techniques that are practiced in MRI sessions such has having participants and researchers take all metal objects off of their person before entering the environment.

Another potential risk is psychological distress caused by being in the enclosed magnet bore. Any participants who find that they become too anxious or uncomfortable during any part of the procedure will be immediately taken out of the scanner and excluded from further scanning.

LP: Potential minimal risks of LP include bleeding and infection and post-spinal headache. It is hard to predict which participants will develop the headache.

EEG: EEGs are safe and painless. The only foreseeable risk is experiencing some itchiness or discomfort from the electrodes on the scalp.

Steps to prevent or to minimize the severity of the potential risks associated with the experimental interventions?

The risks and benefits of CR and tDCS will be explained to participants in detail. After a psychiatric history, participants will undergo clinical and cognitive assessment to assure the clinical appropriateness and safety of their participation. Close clinical monitoring will ensure the appropriateness and safety of their continued participation.

Tele/videoconferencing: Using teleconferencing technology presents a new risk to participant privacy and confidentially. To mitigate this risk, trained research analysts will be using WebEx and Zoom which are approved to be used with participants at CAMH and Sunnybrook respectively. The following mitigation plans will also be put in place to ensure the safeguard of participant information.

- We will ensure that no documents containing personal health information are kept on laptops
- When/If recording the session, then
- We will ensure all participants are aware when recording begins and ends, why recording is necessary, and whether or how it will be shared with participants or made available elsewhere
- If participant does not agree to be recorded, then we will not record the session
- We will remind participants not to discuss, share, or send any identifying information during the session
- We will store the recording in the secure file location for a minimum of 1 year or according to CAMH records retention policy
-

In-Person Visits during the COVID-19 Pandemic: Participating in in-person visits may increase potential exposure to exposure to coronavirus (SARS-2-CoV). To mitigate this risk, everyone will undergo institutional screening procedures prior to and at each visit, adhere to social distancing guidelines of 6 feet, and be required to wear a mask. During the booster sessions where the participants will be attending in-person tDCS+CR training at CAMH and Sunnybrook, one participant and one RA will become in closer contact than 6ft in order to apply the tDCS caps. In addition to a mask, the RA will be required to wear a face shield or goggles when 6 feet distancing is not feasible. The tDCS equipment will be wiped down with disinfectant wipes prior to and after each use. Hand hygiene will be performed before/after each tDCS session and before/after handling tDCS equipment. Disposable nitrile gloves will also be available for use.

Safety Protocol for Remote Visits:

- We will ask participants for an emergency contact number or an alternate phone number to contact them if there is an emergency, or if the call/ virtual session ends inadvertently
- We will ask the participant's address and ask if they are in a fixed location for duration of the call
- Staff will have immediate access to necessary communication technology in order to communicate with relevant research supports or emergency services in case of an emergent research situation
- Check on participant(s) who leave/drop off virtual sessions (i.e., if there is a safety concern) by phone or separate video-conference.

10.1 Benefits:

Participants may benefit from the study if the CR and tDCS procedures to which they are assigned to works. Participants may also benefit from the careful assessment of cognition and close monitoring they will

receive.

12.0 Serious Adverse Events:

A Serious adverse event (SAEs) is any untoward medical occurrence that results in death, is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), results in persistent or significant disability or incapacity, requires hospitalization or causes prolongation of existing hospitalization, results in the development of drug dependency or drug abuse or is an important medical event [defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

SAEs will be collected during the study and will be followed until event resolution, stabilization, or 60 days after the completion of the last participant in the study (whichever comes first).

13.0 Data and Safety Monitoring Plan

A DSMB will be formed to monitor the conduct of the protocol to ensure the safety of participants and validity and integrity of the data. The DSMB will advise the Partners, through the Oversight Committee, on matters pertaining to participant safety, data quality, conduct of the study and its continuation. The DSMB may recommend suspension of funding in the event of early significance of findings or futility, or the determination of unacceptable adverse effects. Dr. Charles Reynolds, Professor of Psychiatry and Neurology at the University of Pittsburgh has agreed to chair the DSMB; and Drs. Carl Pieper, Biostatistician at Duke University, Stephen Pasternak, Neuropsychiatrist at the Robart's Institute and Mustafa Husain, expert in Brain Stimulation at Duke University have agreed to be members of the DSMB.

Members of the DSMB will agree to keep all information confidential. DSMB will review: (i) the number of participants who have been randomized and started treatment, and the number who have completed the protocol; (ii) the amount of data lost, including the reason for loss and the steps taken to avoid such loss in the future; (iii) adverse consequences (whether minor or severe) to any participants together with the short- and long-term remedies to the problem; and (iv) the presence of any new information, especially from this study or from other sources, regarding the expected efficacy and safety of study intervention (or other procedures) used in the study. From these data, the DSMB will make a determination of whether research progress is satisfactory, whether participants' risk/benefit ratio has changed (in which case the REBs will be informed), and whether any changes need to be made to any protocol or procedure. The DSMB members will also be immediately informed when a serious adverse event occur (and is reported to the REBs). The DSMB will also consult with the Data Administrator, requesting the assurance that no breach (or potential breach) of participant confidentiality has occurred and that data archived and quality control procedures are in place and working. The DSMB will write an annual report that will be communicated to the five REBs and the Partners at the annual renewals of the protocol.

14.0 Confidentiality

There is a potential risk of breach of confidentiality that is inherent in all research protocols. Breach of confidentiality will be minimized by the staff and by CAMH Neuroinformatics, who will maintain research data (identified only by participant code number not related to name, or date of birth) in separate charts

and a dedicated password protected electronic database. A list of participant names, their ID numbers, and information about how they can be reached will be kept in a separate locked cabinet with access only to study personnel authorized by the PI. Procedures have been established, and will be followed, to minimize the risk of breach of confidentiality. Procedures to maintain confidentially include: (1) formal training sessions for all research staff emphasizing the importance of confidentiality; (2) specific procedures developed to protect participants' confidentiality, and (3) formal mechanisms limiting access to information that can link data to individual participants. All information obtained from participants will be kept as confidential as possible. Computer based files/data will be entered into password-secured databases and paper-based files will be stored in a secure location. These data will only be accessible to personnel involved in the study and they will abide by confidentiality regulations of the REB.
Only members of the investigative group will have access to secured files or to master lists for participant code numbers and will be well-informed regarding the protection of participants' rights to confidentiality. Identities of participants will not be revealed in the publication or presentation of any results from this project.

Participants will be interviewed specifically to obtain research data. In addition to training and close supervision of research staff and a formal quality control mechanism will provide a systematic check on the quality of interview data.
Clinical information obtained at initial evaluation, and clinical treatment notes, will become part of participants' medical records. Participants will not be identified by name in any publication of research results. Results will be published as group data without the use of characteristics that would identify individual participants. All data pertaining to a participant's involvement in this study will be coded and stored in locked offices. This information will only be accessible to the research team. In unusual cases, a participant's research record may be released in response to a court order. If the research team learns that a participant or someone with whom the participant is involved with is in serious danger or harm, an investigator will inform the appropriate agencies.

Study personnel at each of the five sites will enter study data via a secure database. At point-of-entry, data values will undergo consistency edits (e.g., ID validation, range verification, duplicate detection) and personnel will be required to correct errors. Reports will be created via the Web-based program. Data management staff will run logic error programs to check for accuracy and irregularities within and across

data structures and within and across sites. Quality assurance checks will be conducted daily and weekly by site personnel, as well as by data management staff. Weekly reports will be generated to monitor site data timeliness, completeness, and accuracy as well as participant flow through the study.

15.0 Costs and Payments

Participants will not be charged for research only-services for their participation in this study. All research-only services, such as cognitive assessments, CR and tDCS will be provided to the participant by the study sponsor. Reimbursement will be provided at the end of the study to cover costs of participation ($50 for each MRI, $20 for genetics, $80 for neurocognitive assessment battery, $20 per consent/ baseline visit, and reimbursements for travel costs using TTC tokens/ tickets (associated monetary value when TTC tokens/ tickets have been phased out).

For remote assessments, participants will continue to be compensated at the rate for the completed assessments

and will be provided with an option to receive a cheque via mail or an electronic gift card via email.

16.0 Premature Withdrawal from the Study

Participants are expected to follow all study related procedures and attend all appointments and study visits. Participants may be removed from the study at any time by the investigators if they are unable to follow the study requirements, such as not attending study clinic appointments. Participants may also be withdrawn from the study, at the discretion of the study investigators, if safety of staff or other study members is at risk or of concern.

17.0 Qualifications of Investigators/Staff

Benoit H. Mulsant, M.D., Professor of Psychiatry and clinician scientist at CAMH. He has led or played major roles in a series of multi-investigator and multi-site randomized controlled trials in older participants with depression or dementia. In the past decade, he has also been involved in new efforts to identify biomarkers associated with late-life mental disorders with a focus on pharmacogenetics, neuroimaging, and neurophysiology.

Nathan Herrmann, MD FRCPC, Head, Division of Geriatric Psychiatry, Sunnybrook Health Sciences, Professor of Psychiatry, University of Toronto. Dr. Herrmann's expertise are in the areas of the clinical pharmacology of dementia (treatment of behavioural disturbances and cognition), and the pharmacotherapy of late-life affective disorders. He has published numerous studies on the pharmacotherapy of behavioural disturbances in dementia that involve the use of novel agents, which attempt to determine the underlying neurobiology of these disorders. He has also participated in studies of post-stroke depression examining its neuroimaging and biological correlates.

Bruce Pollock, M.D, PhD, FRCPC., Professor & Head in the Division of Geriatric Psychiatry at the University of Toronto. He is a senior scientist at Centre for Addiction & Mental Health & The Rotman Research Institute and is internationally recognized for his work in geriatric pharmacology. Dr Pollock has vast experience as PI or co-PI of multi-investigator multi-site trials in AD or MDD.

Tarek K. Rajji MD, FRCPC, Associate Professor of Psychiatry is the Deputy Physician-in-Chief of the Geriatric Psychiatry Division at CAMH. He is also a scientist in the Temerty Centre for Brain Intervention. Dr. Rajji is the PI on a psychosocial intervention study in older participants with schizophrenia that includes a cognitive remediation and on two brain stimulation studies, one aims at enhancing neuroplasticity in the DLPFC of participants with schizophrenia, another in AD. These studies are closely related to the approach proposed in this study.

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Appendix 1 – Location of Assessment

Instruments and batteries (text for description)	Location of Assessment	Baseline	Randomization/ Treatment				
		T0	T1	T2	T3 – T8	T9/TX	Other
Structured Clinical Interview for DSM 5 Disorders (SCID) (for depression and alcohol eligibility)	All sites	•					
Socio-Demographic Information	All sites	•					

Montgomery-Asberg Depression Rating Scale (MADRS)	All sites	•		•	•	•	•
NPI-Q	All sites	•		•	•	•	•
Beck Scale for Suicidal Ideation (SSI)	All sites	•	•	•	•	•	•
Modified Hachinski Ischemic Scale	All sites	•		•	•	•	
Handedness Inventory Scale	All sites	•					
Driving Questionnaire	All sites	•				•	
Urine Drug Screen	All sites	•		•			•
Review of Medical History	All sites	•					
Vital signs	All sites	•		•	•	•	•
EKG	All sites	•					
CIRS-G	All sites	•					
Family Questionnaire	All sites	•					
E-COG	CAMH or SHSC	•		•	•	•	
Clinical Dementia Rating (CDR)	All sites	•		•	•	•	
Neuropsych. Battery	CAMH or SHSC	•		•	•	•	
EVLT	CAMH or SHSC	•		•			
2-item version of PASS	CAMH or SHSC	•		•	•	•	
Intervention	CAMH or SHSC			•	•	•	•
LP	CAMH						•
EEG	CAMH	•		•	•	•	•
Genotyping	CAMH – however if subject refuses EEG/ MRI /LP, genetics will be collected at SHSC for the uptown sites						•
MRI	CAMH	•		•		•	
AE/SAE assessment	All sites		•	•	•	•	•