Issue 3, December 2013

positive BRAIN HEALTH NOW

An E-Newsletter about the Positive Brain Health Now cohort study

Developing and testing interventions to improve brain health in HIV

One of the objectives of the Brain Health Now study is to contribute evidence for the acceptability, feasibility, and potential impact of interventions targeting brain health optimization.

This objective will take advantage of the fully characterized platform cohort to draw samples to pilot specific interventions, each under the direction of an expert team, with a common design, sample size and analysis. Three specific interventions will be assessed:

1. Cognitive training
2. Exercise
3. Comprehensive brain health self-management

All interventions will be specifically adapted to the needs of the HIV population through an iterative process involving research participants, community members, and those involved in the front line care of people living with HIV.

This newsletter provides details on special aspects of the computerized cognitive training intervention, which will be developed by : Drs. Etienne De Villers-Sidani, Lesley Fellows, Marianne Harris, Lisa Koski, Alain Ptito and Nancy Mayo.

Continues on Page 2

Key updates

Recruitment is going well at the Montreal Chest Institute !

So far, 340 patients have been invited to participate in the BHN study, about half have agreed to meet with the Research Assitant to know more about the study and the vast majority of these patients have agreed to participate.

Our first article on Brain Health has been published in the on-line magazine Positivelite.com! Have a look at:

http://dld.bz/ddJu5

Our new website is now live ! come visit us at:

http://brainhealthnow.mcgill.ca

What's coming down the pipeline ?

Recruitment at other investigative sites participating in the BHN study, will start at the beginning of 2014.

WHY IS COGNITIVE TRAINING IMPORTANT IN HIV?

Cognitive deficits in HIV may reflect degraded brain network functioning, due to a combination of brain health insults: some generic (aging), some HIV-specific (inflammation, diffuse demyelination and inherent vulnerability that varies across individuals).

Consistent with this hypothesis, the cognitive domains most affected are those that rely on extended networks (e.g. attention and executive functions relying on fronto-parietal and fronto-striatal circuits), exquisite timing (psychomotor function), or both. These network-based cognitive functions are vulnerable, but they are also resilient: there is a high degree of learning-dependent plasticity in networks involving the frontal lobes (1-4). This argues that the cognitive deficits in HIV may be amenable to remediation through cognitive training, and suggests mechanisms by which this might occur.

There are many forms of cognitive rehabilitation; approaches that take advantage of advances in the understanding of the mechanisms of neuroplasticity and the neural systems supporting human cognition are likely to be highest yield (5, 6).

Continues on Page 3

Dr. Etienne de Villers-Sidani

Dr. de Villers-Sidani is a neurologist specializing in cognitive disorders. He has a particular interest in understanding the role of sensory experience and brain plasticity in the emergence and remediation of cognitive impairments. His laboratory uses electrophysiological techniques to determine how sounds and auditory training both shape cortical circuits and alter the perception of sounds, and their use in memory and decision-making. His main goal is to develop novel therapeutic strategies that can improve cognitive function in patients suffering from conditions related to abnormal sensori-motor processing : dementia, age-related cognitive decline, stroke, traumatic brain injuries, among other conditions.

Dr. De Villers-Sidani will be the academic leader responsible for the computerized training intervention sub-study.

HOW WILL COGNITIVE REHABILITATION BE ASSESSED ?

This sub-study will make use of Plasticity-based Adaptive Cognitive Remediation (PACR), a promising new therapeutic tool for the recovery to cognitive function in HIV. Conceptually, PACR applies well-understood techniques derived from brain plasticity and implicit/procedural/perceptual learning to improve the speed and accuracy of information processing, with exercises that are designed to drive generalized improvements. Simultaneously, these exercises heavily engage neuromodulatory systems to re-establish their normal control over learning and memory. As an individual restores these degraded abilities through intensive procedural learning, the encoding of naturalistic information significantly improves, and all resulting declarative memory and cognitive functions based on the quality of that incoming information necessarily improve as well, leading to improvement that generalizes beyond the trained tasks. Multiple randomized controlled studies have now demonstrated that PACR improves cognitive and functional abilities in patient populations with cognitive dysfunction similar in type and magnitude to patients with cognitive deficits due to HIV (5,7, 8-10) .

STUDY DESIGN

A subset of 60 HIV+ individuals with both cognitive symptoms and a B-CAM ≤ 1.5 will be randomly drawn from the main study population within one month of having completed a routine study visit. Half will be randomly assigned to the PACR training, the other half to a control group who will have a re-iteration of the brain health education material supplied with the main study, with additional encouragement to choose one brain health goal from this material and try to make positive change over the sub-study (8 week) period. All will return for an in-clinic post-intervention assessment, where they will complete the B-CAM, within 4 weeks of completion of the intervention. After completion of this extra evaluation, the control group will be given the option of accessing the PACR training for 8 weeks, without having to come in for any further testing.

Inclusion criteria

- B-CAM ≤ 1.5
- Able to have convenient daily access to the Internet
- Stable medical condition
- Have been on a stable HAART regimen for > 6 months
- Have not had a change in medications that could potentially interfere with cognition in the past 4 months.

Exclusion criteria

- Past history of CNS opportunistic infection or stroke
- Current substance dependence or abuse (as per DSM-IV criteria) within the past 12 months.

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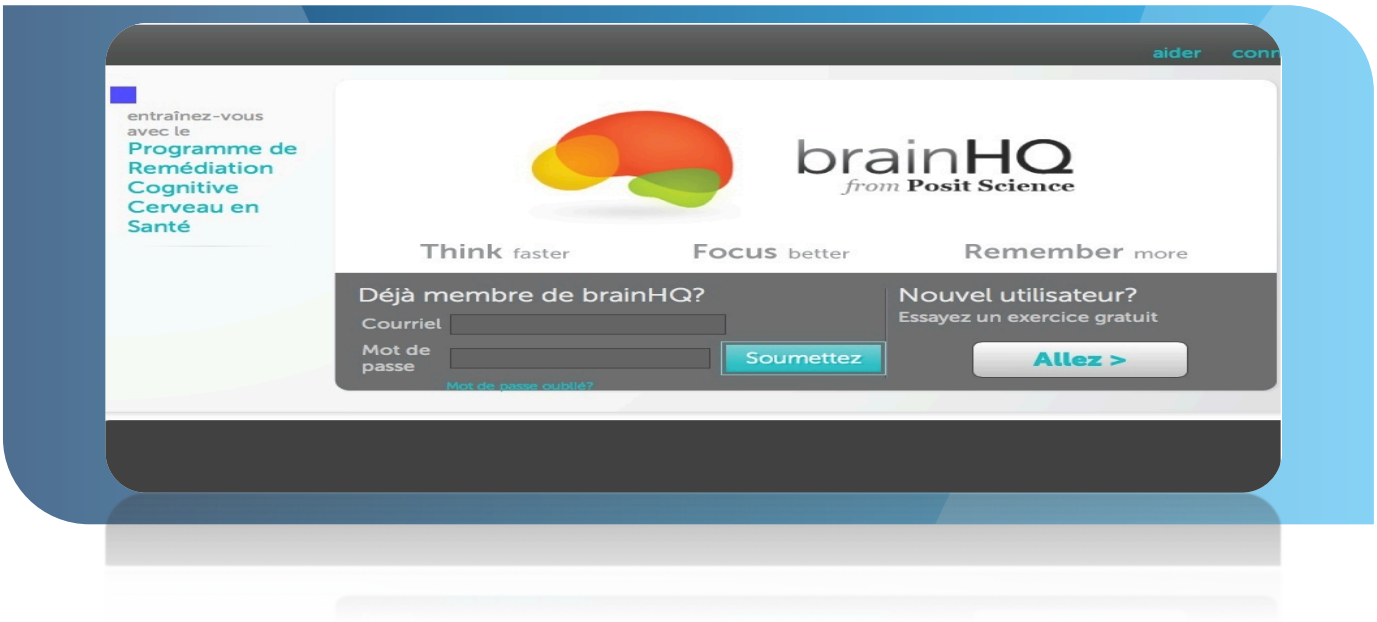


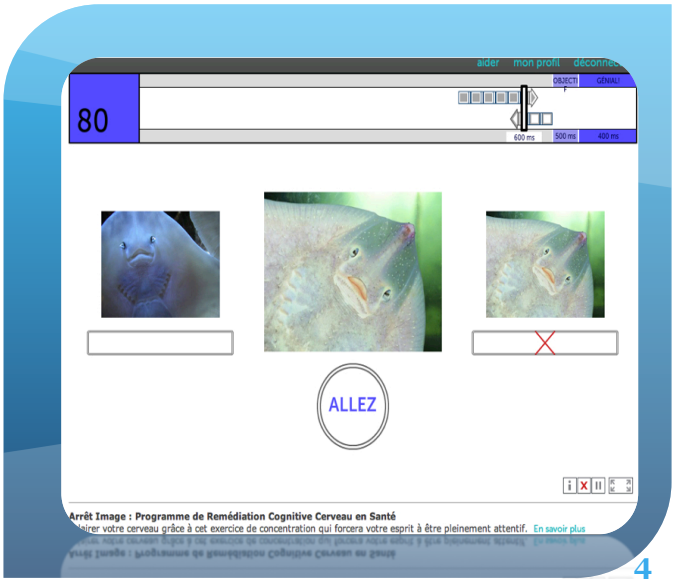
TRAINING PROGRAM

PACR runs in a web browser on any Internet connected computer and is implemented in an engaging game-like format. The training program is administered online (including consent to participate in the study): the participant opens a standard web browser on a broadband-connected computer and goes to the PACR study web site (following a link from the Brain Health project's website). The participant then logs into the PACR (using a study-provided screen name that contains no personally identifiable information).

A game-like experience begins, where the participant is encouraged to earn points and in-game rewards to advance. To do so, the participant selects one of the cognitive exercises scheduled for the day, and performs that exercise for fifteen minutes. Participants perform tens to hundreds of trials over the course of the fifteen-minute session, with each trial providing auditory and visual feedback to indicate if the trial was performed correctly or incorrectly.

The training is individually tailored to maximize its effectiveness. Summary screens including game metrics (points, levels) and exercise metrics (usage, progress) are shown to the participant at the end of each session.

The scheduling mechanism ensures that a patient progresses through the exercises in a defined order, generally moving from more simple (early sensory processing) exercises to more complex (multimodal, cognitive control) exercises over the course of the 8-week experience. At any point in time, the participant only has access to a subset (typically six) of these exercises, four of which are performed per day.



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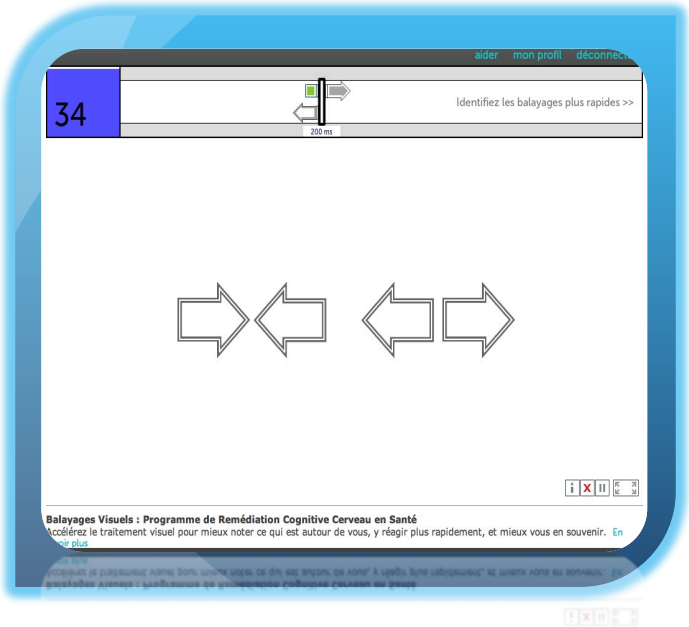

Each exercise has specific criteria for completion, and after those criteria are met the exercise is removed from the active set and the next exercise added. This mechanism ensures both ongoing novelty and engagement for the participant, and that the participant progresses smoothly through the complete set of exercises over the program use period.

Free access will be provided to the PACR program, with a tailored cognitive training program available in both French and English, specifically targeting domains and mechanisms that are most affected in HIV.

STATISTICAL ANALYSIS AND SAMPLE SIZE ESTIMATION

Basic descriptive statistics will be used to characterize the study sample, and to assess the feasibility and acceptability of the PACR judged by the number of sessions completed, and the presence of improvement in training performance over the 8-week period. B-CAM scores will be compared between PACR and control groups. The outcome will be responder status (defined as improvement of >0.5 logits) on the B-CAM. An intervention and a control group will be assembled each with a sample size of 30 participants.

The observed responses in the intervention and control groups will provide more accurate estimates to plan for a scale up of this work to a full trial. An exploratory analysis will evaluate response in only those who completed at least 60% of the training sessions, recognizing that power here will be reduced, but the information nonetheless important.

The intervention group will also be compared to all those eligible for randomization to this intervention in the platform as a whole.

Additional analyses will be used to explain changes in B-CAM score as a function of changes expected from the intervention. As the intervention cohort is small, we will use concordance parameters, rather than a regression model, to quantify the degree to which changes in hypothesized mechanisms by which the interventions operate are concordant (at the individual level) with changes in the outcomes (cognitive ability).

Continues on Page 6

Dr. Marianne Harris

Dr. Harris received her MD from the University of Alberta, Edmonton, Alberta. Postgraduate training included a residency in Family Medicine at the University of Alberta and a postdoctoral fellowship in HIV/AIDS research with the Canadian HIV Trials Network at Montreal General Hospital.

She is a Clinical Research Advisor for the AIDS Research Program at St. Paul's Hospital in Vancouver, British Columbia, Canada. Her primary areas of interest are HIV clinical trials and the complications of antiretroviral therapy. She is currently Program Director, ABC's of HIV Treatment and Care, B.C. Centre for Excellence in HIV/AIDS.

Dr. Harris is the Principal Investigator for the Brain Health Now study at St-Paul's Hospital, John Ruedy Immunodeficiency Clinic (IDC).

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