Computer-based cognitive intervention for aphasia: Behavioural and neurobiological outcomes

Background

Aphasia, an acquired impairment of language that commonly occurs after stroke, can have significant consequences on all aspects of functioning of affected individuals. Some have proposed that the language deficits observed in aphasia are due to underlying limitations in cognitive processes that support language[1-3]. This 'cognitive' theory of aphasia is gaining increased attention in the research literature[4], and is the impetus for the study of treatments for aphasia that target these underlying cognitive processes[5-8]. Indeed, studies of cognitive interventions in healthy populations have reported positive outcomes in behavioural (i.e. language and overall cognitive functioning[9, 10]) as well as neurobiological (i.e., brain function and/or structure[11-13]) domains, offering promise for the application of these types of interventions to aphasia.

Recently, computer-based 'brain training' programs have become increasingly prevalent. *BrainFitness (BF)* is one such commercially available program; it has been used to show improvement in auditory processing speed, attention and working memory in typically aging adults[14, 15]. This program has the potential to be a useful intervention for individuals with aphasia, but questions regarding the clinical utility of the program and neural correlates of training-related behavioural changes remain. The purpose of this study was to investigate the effect of *BF* training in people with aphasia using behavioural and neurobiological outcome measures.

Method

Participants. Three participants with aphasia as a result of stroke participated in this study. All participants passed screenings of vision and hearing, and had sufficient dexterity to operate a computer mouse. Demographic characteristics, aphasia type and lesion descriptions are presented in Table 1.

Intervention. The *BF* program comprises 40 hours (1 hr/day x 5 days/week x 8 weeks) of training on 6 modules targeting processing, attention and working memory in the auditory modality. The modules range from simple tone discrimination to remembering facts heard during conversational discourse. Modules gradually increase in complexity by varying: a) number and type of stimuli (tones, syllables, non-words, real words); b) duration and acoustic properties of the stimuli; c) rate of presentation of stimuli; and d) task demands. The program is designed to be responsive to the user to maintain an 85% accuracy rate. For example, in the first module that targets auditory processing speed, tones are presented that are relatively easy to process (loud and long). As the participant's performance improves, the stimuli gradually become more complex (softer and shorter). Table 2 presents a description of each training module. Participants completed the intervention under the direction of a speech-language pathologist (SLP), who was present during the first 10 hours of training. Subsequently, the SLP monitored participants'

compliance and progress through an online portal and checked in at least once/week by telephone.

Neuroimaging. Functional neuroimaging data was conducted using a 1.5T Siemens MRI. Functional BOLD images were acquired using a spin-echo echo-planar imaging sequence with the following parameters: a 90° flip angle, TR = 1970 ms TE = 40 ms, number of slices = 36, base resolution 64 x 64, voxel size 4x4x4 mm. Participants completed an auditory sentence plausibility judgment task during scanning, and indicated their responses by pressing one of two buttons (yes/no) with their left hand.

Outcome Measures. Behavioural and neuroimaging assessment was conducted at *baseline* (8 weeks pre-treatment), immediately *pre-treatment* and immediately *post-treatment*. The primary behavioural outcome measure was % improvement on the 6 *BF* training modules; secondary measures comprised scores on the *Western Aphasia Battery-Revised* (WAB-R[16]) and the *Cognitive-Linguistic Quick Test* (CLQT[17]). Neurobiological outcomes were measured using graph network analyses modeling functional connectivity (i.e., partial correlations based on % signal change of the BOLD response during task vs. rest) between pre-determined regions of interest (ROIs) during completion of an auditory sentence plausibility judgment task. ROIs were chosen based on Hickok and Poeppel's[18] model of auditory language processing.

Results

Behavioural Results. As seen in Figure 1a, all participants demonstrated within-program gains in the various cognitive domains targeted by *BF*. However, on secondary outcome measures, participants did not exhibit stable baseline performance (Fig 1b), which is problematic for interpreting treatment-related changes. This variability may be due in part to the fact that different clinicians (including student clinicians) completed the assessments at each time point. Nonetheless, only examining pre- and post-treatment timepoints may give false interpretations of treatment gains, given a stable baseline in behavioural performance was not observed.

Neuroimaging Results. Figures 2-4 present graphical models representing functional connectivity between brain regions outlined in Hickok & Poeppel's[18] model (see Appendix 1 for details), in conjunction with activation maps for each participant. Edges (lines) represent partial correlations between the average time series in each pair of brain regions, with color depicting direction of correlation (black = positive, red = negative) and line thickness depicting strength of correlation. (Note: RJ's graphs depict only right hemisphere ROIs, due to her extensive left hemisphere lesion; only pre-treatment and post-treatment neuroimaging results are available for RJ). Participants demonstrated changes in functional connectivity patterns between all timepoints. However, particularly for RD and TH for whom two baseline assessments are available, it is evident that connectivity between ROIs within the language processing network has changed post-treatment relative to baseline and pre-treatment. Notably, all three participants demonstrated increased connectivity between posterior superior temporal gyrus (pSTG) and posterior superior temporal sulcus (pSTS) (in the right hemisphere for RJ and left hemisphere for RD and TH) at post-treatment that was not evident at pre-treatment.

Discussion

Three participants with aphasia underwent 40 hours of training using a commercially available computer-based cognitive training program (*BrainFitness*). Participants demonstrated behavioural improvements on cognitive processes targeted by the *BF* program, yet generalization to non-trained domains remains to be seen. Given the inherent variability in aphasic language performance, these data point to the need for multiple assessment points in treatment outcomes research.

A novel technique for examining changes in functional connectivity (graph network analysis) illustrated changes in regions of interest that are part of well-characterized auditory processing networks. Specifically, connections between pSTG and pSTS representing the initial ROIs along the dorsal language-processing route, active during formulation of articulatory-based responses from acoustic input[18-20] were noted in all participants. We hypothesize that the repeated sub-vocalization participants engaged in during training tasks served to increase connectivity between these regions along the dorsal route. Interestingly, both TH and RD (who were fluent and less severe in their behavioural and lesion profiles) demonstrate 'tightening up' of overall functional connectivity at post-treatment relative to pre-treatment and baseline. At post-treatment, the number of edges has decreased and those that remain correspond to regions along dorsal and ventral language processing routes proposed by previous investigators[18-20].

Despite the limitations of this preliminary study*, three important lessons can be learned from this research: 1) Multiple baseline assessments of behavioural and neuroimaging data should be incorporated into studies investigating treatment outcomes; 2) Graph network analyses may be a useful technique for investigating functional changes related to treatment; 3) Dynamic brain networks may be observed following cognitive intervention in the face of (relatively stable) behavioural performance. This last point highlights the need for more investigations on the time course of treatment-induced neuroplastic changes.

*We have collected data from two additional participants, addressing the issue of multiple assessors and using additional secondary behavioural outcome measures, which we will have analyzed to present at the conference.

 (1193 words)

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Appendix

Functional Connectivity (Graphical Model) Analysis

In order to estimate the functional connectivity network structure between brain regions we first average the time series of voxels within each brain region. In this work, we represent the functional connectivity structure by a graphical model. Graphical models display the dependency structure of a set of pre-defined brain regions using a graph G. A graph, G=(V,E), consists of a set of vertices V and corresponding edges E that connect pairs of vertices. They may be defined as either undirected or directed with respect to how the edges connect one vertex to another. Directed graphs infer directionality between variables (or vertices) while undirected graphs do not, and in this work we focus exclusively on the latter. Here each vertex represents a brain region and edges encode dependencies between the variables.

In this work, we estimate the undirected graph using the graphical lasso (Friedman et al.[24]). Here an edge and missing edge between two vertices in the graph indicates a partial correlation and conditional independence between brain regions respectively. The graphical lasso assumes that the network structure is sparse. It is based on a penalized likelihood where the sparsity of the graph is controlled by a parameter, λ. We estimate the undirected graph for a path of λ values and choose the value of λ (sparsity of the graph) based on minimizing the Bayesian Information Criterion (BIC). After estimating the graph based on BIC minimization and identifying non-zero edges, the model is refit without the sparse inducing (or l_1) constraint while keeping the zero elements in the matrix fixed to reduce bias and improve the model selection performance. As the graphical lasso is known to estimate a number of false positive edges in the estimated undirected graphs, we perform a bootstrap inferential procedure similar to the subsampling stability selection approach of Meinshausen and Bühlmann[25]. The goal is to control the familywise type I multiple testing error by looking at the selection probabilities of every edge under subsampling. In this setup, the data are bootstrapped many times and we choose all edges that occur in a large fraction of the resulting selection sets. We thereby retain edges with a high selection probability and remove those with low selection probabilities. We used a bootstrap threshold, π_{thr}, of 0.95 in the estimated undirected graphs in Figures 2-4. In other words, each edge in the undirected graphs was non-zero in 950 out of 1,000 bootstrap samples of the data.

Table 1. Demographic information, aphasia type and lesion description of three participants

	Demographics	Aphasia Type	Lesion Description
RJ	53/F; 14 yrs education; 5 yrs post-onset	Non-fluent (Broca's)	Large lesion affecting grey and white matter across frontal, temporal and parietal cortex
TH	67/M; 8 yrs education; 4 yrs post-onset	Fluent (Anomic)	Cortex & sub-adjacent white matter in angular gyrus, posterior MTG and STG
RD	67/M; 8 yrs education; 4 yrs post-onset	Fluent (Anomic)	Cortex & sub-adjacent white matter in anterior MTG, STG, insula and subcortical structures

Table 2. *BrainFitness* training modules

Title of Module (Targeted Process)	Description
Sound Sweeps (Processing Speed)	Rising/falling tones are presented; participant pushes a up/down button to indicate which one was heard
Fine Tuning (Sound Discrimination)	An auditory stimulus (syllable/word) is presented with 2 written choices (minimal pairs; i.e. syllables that differ in one sound); participant chooses correct item
Memory Grid (Sound Precision)	Visual tokens are presented in a 'memory game' format. When clicked, a stimulus (syllable/word) is presented auditorily; participant must correctly match stimulus pairs
Syllable Stacks (Sound Sequencing)	Visual syllables/words stimuli are displayed; participant hears a sequence of corresponding auditory stimuli and selects the stimuli in the order they were presented
To-Do List Training (Working Memory)	A grid of pictures are displayed; participant hears auditory instructions and chooses the pictures in the correct order (e.g. first, choose the hammer, then the rope)
In the Know (Narrative Memory)	Participant hears a series of facts as if listening to a conversation and subsequently answer a series of multiple choice questions

Figure 1. Behavioural gains demonstrated by participants RJ, TH and RD following 40 hours of *BrainFitness* training. A. Within-program gains following *BF* training. Bars represent percent improvement on each of 6 cognitive modules targeted by the program. B. Improvement on standardized measures of language (*WAB-R*) and cognitive function (*CLQT*) following training.
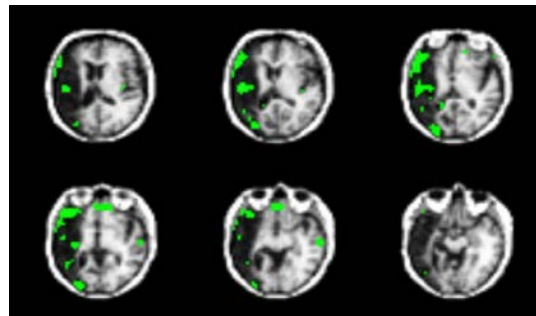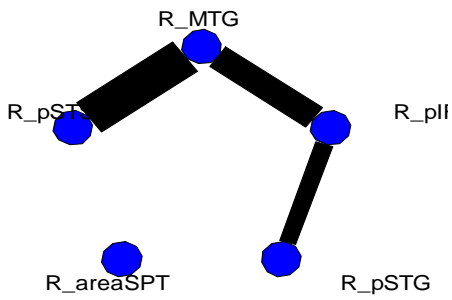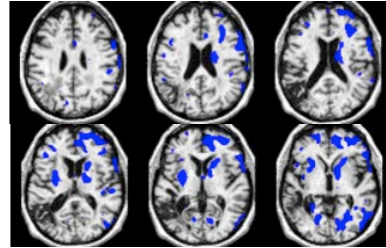
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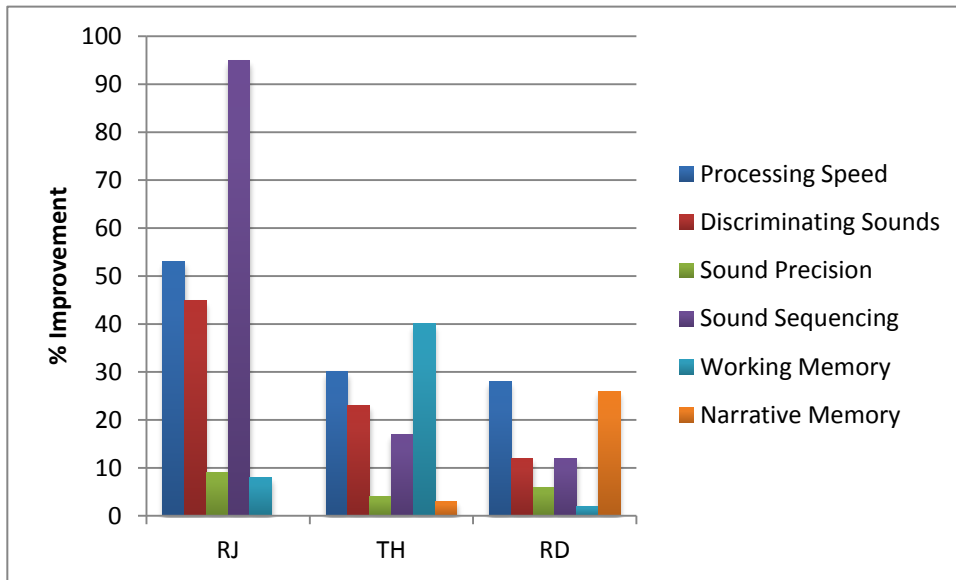
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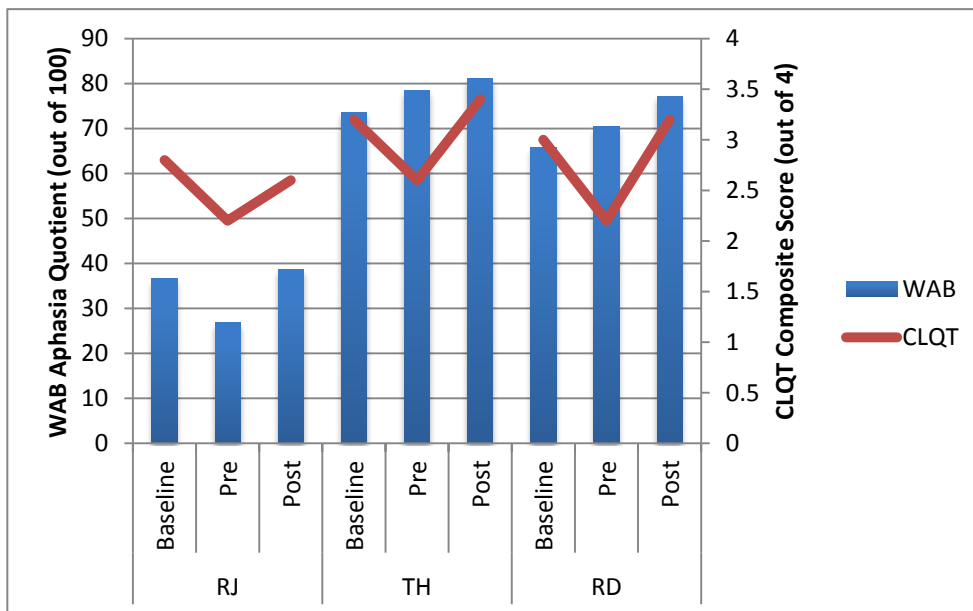
Figure 2. Graph metric and activation maps representing functional connectivity and activation, respectively, during sentence plausibility judgement task for participant RJ. (Only pre- and post-

treatment neuroimaging results are available for RJ. Increased connectivity between right pSTS and pSTG is evident at post-treatment, suggesting efficient processing along the dorsal language processing route.
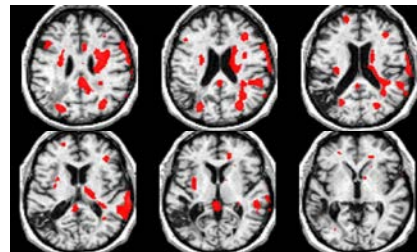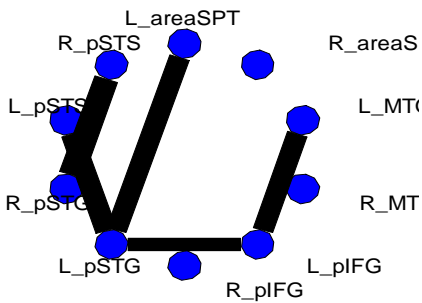
Pre-Treatment

Post-Treatment
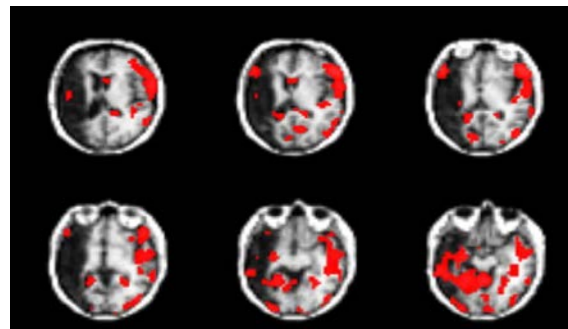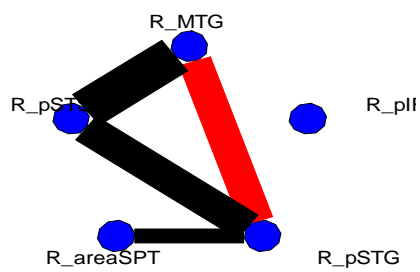
Figure 3. Graph metric and activation maps representing functional connectivity and activation, respectively, during sentence plausibility judgement task for participant TH. Increased connectivity between left pSTS and pSTG as well as a 'tightening up' of overall functional connectivity is evident at post-treatment, suggesting more efficient processing along the dorsal language processing route.
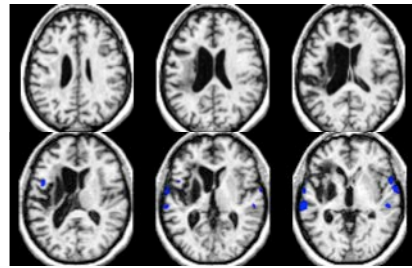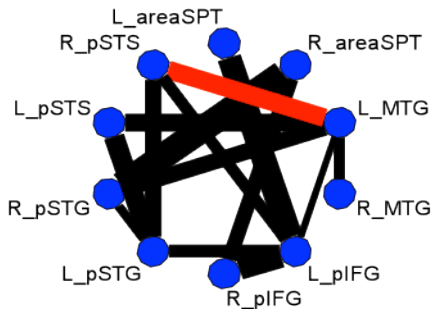
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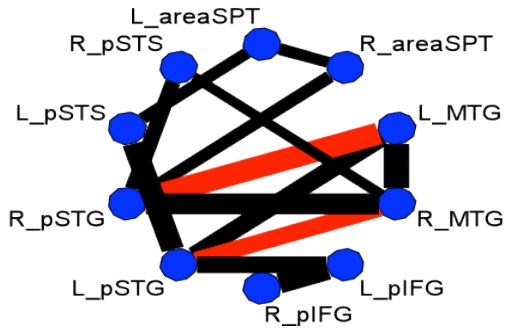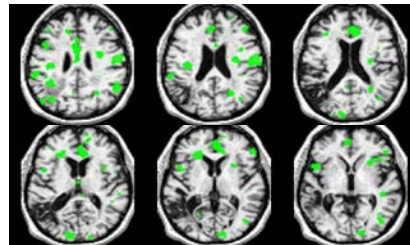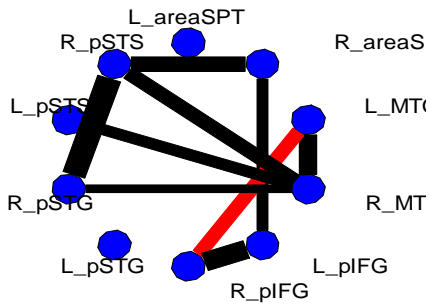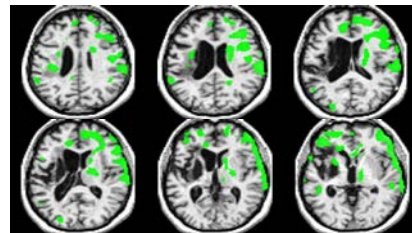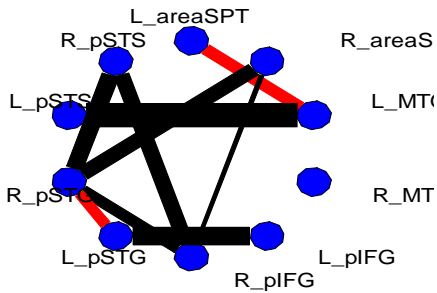

Pre-Treatment

Post-Treatment

Figure 4. Graph metric and activation maps representing functional connectivity and activation, respectively, during sentence plausibility judgement task for participant RD. Increased connectivity between left pSTS and pSTG as well as a 'tightening up' of overall functional connectivity is evident at post-treatment, suggesting more efficient processing along the dorsal language processing route.

Baseline

Pre-Treatment

Post-Treatment