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How does iReadMore therapy change the reading network of patients with central alexia?

Sheila J Kerry[1], Oscar M Aguilar[2,3,4], William Penny[5], Jennifer T Crinion[1], Alex P Leff[1,2,3] and Zoe V J Woodhead[2,6]

[1]*Institute of Cognitive Neuroscience, University College London, UK, WC1N 3AZ.*
[2]*Department of Brain Repair and Rehabilitation, Institute of Neurology, University College London, UK*
[3]*The Wellcome Centre for Human Neuroimaging, University College London, UK, WC1N 3BG*
[4]*Facultad de Psicología, Pontificia Universidad Javeriana, Colombia*
[5]*School of Psychology, University of East Anglia, Norwich NR4 7TJ*
[6]*Department of Experimental Psychology, University of Oxford, UK, OX1 3AQ*

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Corresponding author: Sheila Kerry, Institute of Cognitive Neuroscience, 17 Queen Square, London WC1N 3AZ, sheila.kerry.11@ucl.ac.uk

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Running title (50 characters): Reading network modulation in central alexia

Sheila J Kerry*[1], Oscar M Aguilar[2,3,4], William Penny[5], Jennifer T Crinion[1], Alex P Leff[1,2,3] and Zoe V J Woodhead*[2, 6]

Author affiliations:

[1] Institute of Cognitive Neuroscience, University College London, UK, WC1N 3AZ.

[2] Department of Brain Repair and Rehabilitation, Institute of Neurology, University College London, UK

[3] The Wellcome Centre for Human Neuroimaging, University College London, UK, WC1N 3BG

[4]Facultad de Psicología, Pontificia Universidad Javeriana, Colombia, 110311.

[5]School of Psychology, University of East Anglia, Norwich NR4 7TJ

[6] Department of Experimental Psychology, University of Oxford, UK, OX1 3AQ

Corresponding author:

Sheila Kerry, Institute of Cognitive Neuroscience, 17 Queen Square, London WC1N 3AZ, sheila.kerry.11@ucl.ac.uk

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Abstract

Central alexia (CA) is an acquired reading disorder co-occurring with a generalised language deficit (aphasia). The roles of perilesional and ipsilesional tissue in recovery from post-stroke aphasia are unclear. We investigated the impact of reading training (using iReadMore, a therapy app) on the connections within and between the right and left hemisphere of the reading network of patients with CA. In patients with pure alexia, iReadMore increased feedback from left inferior frontal region (IFG) to the left occipital (OCC) region. We aimed to identify if iReadMore therapy was effective through a similar mechanism in CA patients.

Participants with chronic post-stroke CA (n=23) completed 35 hours of iReadMore training over four weeks. Reading accuracy for trained and untrained words was assessed before and after therapy. The neural response to reading trained and untrained words in the left and right OCC, ventral occipitotemporal (vOT) and IFG was examined using event-related magnetoencephalography.

The training-related modulation in effective connectivity between regions was modelled at the group level with Dynamic Causal Modelling.

iReadMore training improved participants' reading accuracy by an average of 8.4% (range: -2.77 to 31.66) while accuracy for untrained words was stable. Training increased regional sensitivity in bilateral frontal and occipital regions, and strengthened feedforward connections within the left hemisphere. Our data suggests that iReadMore training in these patients modulates lower-order visual representations, as opposed to higher-order, more abstract ones, in order to improve word reading accuracy.

Significance Statement

This is the first study to conduct a network-level analyses of therapy effects in participants with post-stroke central alexia. When patients trained with iReadMore (a multimodal, behavioural, mass practice, computer-based therapy), reading accuracy improved by an average 8.4% on trained items. A network analysis of the magnetoencephalography data associated with this improvement revealed an increase in regional sensitivity in bilateral frontal and occipital regions and strengthening of feedforward connections within the left hemisphere. This indicates that in CA patients iReadMore engages lower-order, intact resources within the left hemisphere (posterior to their lesion locations) to improve word reading. This provides a foundation for future research to investigate reading network modulation in different CA subtypes, or for sentence level therapy.

Introduction

Central alexia (CA; also known as Alexia with agraphia (Dejerine, 1891)) is a reading disorder that occurs within the context of a generalised language disorder (aphasia). Patients with CA find reading slow and effortful and make frequent errors (Leff and Starrfelt, 2013). There is no agreed treatment for CA and to date there have been no group-level investigations of how neural plasticity may support reading recovery in patients with CA. In Woodhead et al., (2018) we demonstrated that a computerised word reading therapy app improved word reading in 21 patients with CA. The aim of this cross-modal training was to co-activate orthographic, phonological and semantic representations of the word in order to rebuild the neuronal connections between them. The present study aimed to improve our understanding of the therapeutic mechanisms in CA, with a view to developing stratified therapy pathways in future.

After left hemisphere stroke, the role of spared ipsilesional regions and right hemisphere homologues in supporting aphasia recovery are unclear (Adair et al., 2000; Tsapkini et al., 2011; Crinion and Leff, 2015; Hartwigsen and Saur, 2017). There is evidence for functional reorganisation in spared left hemisphere regions (Jobard et al., 2003; Fridriksson, 2010; Abel et al., 2014, 2015; van Hees et al., 2014; Bonilha et al., 2016; Pillay et al., 2017); while other studies have identified right hemisphere homologues fulfilling this function (Meinzer et al., 2006; Richter et al., 2008; Lee et al., 2017) both accounts may be correct and aphasia recovery may rely on a combination of mechanisms (Saur et al., 2006; Kurland et al., 2008; Turkeltaub et al., 2011; Crinion and Leff, 2015; Mohr et al., 2016). We modelled a bilateral reading network in patients with CA to ascertain the effects of therapy within and between the hemispheres.

While post-stroke aphasia is the result of focal damage, it is increasingly viewed as a network disorder (Hartwigsen and Saur, 2017). Neuroimaging studies of skilled readers show that word reading activates a predominantly left-lateralised network of occipitotemporal, temporal and inferior frontal areas (Heim et al., 2005; Graves et al., 2010; Price, 2012; Carreiras et al., 2014; Hoffman et al., 2015; Perrone-Bertolotti et al., 2017; Xu et al., 2017; Zhou and Shu, 2017). The local combination detector (LCD) model of visual word recognition suggests that because neurons are tuned to progressively larger fragments of a word as their location moves anteriorly, word reading is achieved primarily through feed-forward processing along the visual ventral stream (Dehaene et al., 2005). However, an alternative account suggests that efficient word recognition relies on interactive feedforward (bottom-up) and feedback (top-down) processing within this network (Cornelissen et al., 2009; Wheat et al., 2010; Price and Devlin, 2011; Woodhead et al., 2014). Dynamic causal modelling (DMC) identifies the causal influence of one region upon another, allowing us to explore the interaction between top-down and bottom-up processes.

Within the domain of reading rehabilitation, in participants with pure alexia (typically caused by left posterior cerebral artery (PCA) stroke), reading training was associated with stronger connectivity within the left hemisphere, and increased top-down connectivity from frontal to occipital regions (Woodhead et al., 2013). This was interpreted as evidence that predictions from phonological and/or semantic representations in left frontal cortex facilitated visual word recognition after training. However, in CA (typically caused by left middle cerebral artery (MCA) stroke), these ‘central’ language representations are damaged or disconnected.

As there is little in the existing literature to guide predictions of network reorganisation following therapy in CA, we based our hypothesis on what is known about the reading network in healthy controls and pure alexia. The training employed iReadMore, an adaptive word reading training app which improved word reading ability for trained items in pure alexia (Woodhead et al., 2013) and CA (Woodhead et al., 2018). Using DCM of magnetoencephalography (MEG) data we investigated how effective connectivity within the reading network changed as a result of therapy. Our speculative hypothesis was that training would strengthen feedback connections within the left hemisphere, and the left IFG’s self-connection. It is anticipated that these analyses will yield predictions for future investigations of how neural network plasticity supports language recovery.

Method

Study design

A within-subject, repeated measures design was used. The data presented here were acquired during a larger crossover study that assessed the effects of iReadMore therapy and transcranial direct current stimulation (tDCS) on single word reading (Woodhead et al., 2018). Participants completed an MEG scan before (T3) and after (T4) a four-week reading therapy block (see Figure 1). Additionally, two baseline language assessments were conducted four weeks prior to training (T1 and T2) and at two time points after training T5 and T6.

During the therapy block participants were asked to amass ~35 hours of iReadMore training, through 40-minute face-to-face sessions attended three times per week (Monday, Wednesday and Friday; 11 sessions in total) supplemented with independent use at home.

The effect of tDCS was not analysed in this paper as, a) it was not designed to be tested using a between subjects design, as would be required in the current analysis and b) the effect size of tDCS was small compared to the main effect of iReadMore.

Testing and face-to-face therapy sessions were conducted at the Institute of Cognitive Neuroscience, University College London.

Participants

Twenty-three participants with CA (15 males, mean age 52 years, range 26-78 years, see Table 1 for demographic information), diagnosed by a neurologist or speech and language therapist, were recruited from either the PLORAS stroke patients database held at the The Wellcome Centre for Human Neuroimaging

(Seghier et al., 2016), or speech and language therapy services at the National Hospital for Neurology and Neurosurgery, University College London Hospitals.

The following inclusion criteria were used: i) left-hemisphere middle cerebral artery stroke with at least partial sparing of left IFG; ii) greater than 12 months post-stroke; iii) dominant English language use in activities of daily living; and iv) CA, operationalized as impaired word reading (CAT word reading T-score <61) and impaired spoken language (CAT naming <63 or picture description <61). Screening and diagnoses were conducted historically in a clinical setting (data available on request from authors), but additional baseline tests (as described in Woodhead et al., 2018) were performed at the start of the trial, including CAT Naming, non-word reading and word reading (Table 1).

Exclusion criteria included: i) premorbid history of neurological or psychiatric illness; ii) history of developmental language disorder; iii) severe spoken output deficit and /or speech apraxia (CAT repetition <44); iv) seizures in the past 12 months; v) contraindications to MRI scanning; and vi) extensive damage to left IFG.

Participants were classified as having phonological (n=13), deep (n=9) or surface dyslexia (n=1) according to the pattern of word and non-word reading performance at baseline, using criteria described by Whitworth *et al.,* 2014 (for further details, see Woodhead *et al.,* 2018). The low proportion of patients with surface dyslexia is consistent with an opportunity sample of stroke patients described by Brookshire et al. (2014).

The participant information sheet was provided in written and auditory forms. All participants gave informed written consent in accordance with the Declaration of Helsinki. The Queen Square Research Ethics Committee approved this project.

Structural MRI

T1 weighted MRI scans were obtained in a 3.0T whole body MR system (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany) equipped with a standard 32 channel head coil radiofrequency (RF) receiver and RF body coil for transmission.

Data were pre-processed using Statistical Parametric Mapping 12 (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) mounted in Matlab 2014b (The Math- Works Inc.; Natick, MA, USA). Magnetic transfer (MT) maps were obtained for each participant using SPM12's Voxel Based Quantification (VBQ) toolbox (Weiskopf et al., 2013; Callaghan et al., 2014). The MT maps were spatially normalized into standard MNI space and segmented into tissue types (e.g. grey and white matter, cerebrospinal fluid, atypical or lesion). Lesions were identified using SPM12's Automated Lesion Identification toolbox (Seghier et al., 2008). This compared CA participant's segmented MT maps to the MT maps of 29 healthy controls. A binary lesion image was created for each CA participant, upon which candidate dipole location solutions could be compared. Across our group of participants, lesion location was predominantly within the territory of the left middle cerebral artery, centred on the supramarginal gyrus (Figure 2B).

iReadMore training

For a more detailed description of iReadMore training see Woodhead et al., 2018. Briefly, iReadMore aims to retrain whole word reading by repeatedly exposing the user to pairings of written and spoken words, and an associated picture. The aim of this cross-modal training is to co-activate orthographic, phonological and semantic representations of the word in order to rebuild the neuronal connections between them. iReadMore was administered on a tablet computer. The software cycled through 'training' and 'challenge' phases. During the training phase, participants were presented with 10 face-down cards. On selection, the reverse of the card revealed the written word, spoken word and a picture of the word (all congruent with each other).

The challenge phase consisted of up to 30 trials. In each trial a written and spoken word were presented simultaneously. In half the trials the words were different (incongruent). Participants made same/different judgements via a button press and points were accrued for correct responses. If a criterion score was reached they passed the level. The algorithm within the iReadMore software adjusted task difficulty based on the user's performance. This modifies: i) the similarity between the target spoken word and the written foils in the challenge phase (three levels); ii) the exposure duration of the written words (from a maximum of 4000ms to a minimum of 100ms); and, iii) the criterion score required to pass a level.

Training stimuli

High frequency words ($SUBTLEX_{WF}$>50) of three to six letters were drawn from the SUBTLEX database (Brysbaert and New, 2009). Two matched lists of 180 words were created. For each word on the A list there was a corresponding word on the B list matched for letter length, syllable length, written frequency and imageability.

Over two baseline sessions (T1 and T2), CA participants completed an assessment of the entire word corpus whereby they read each word out aloud. Based on each participant's baseline performance (word reading accuracy and speed), a customised set of 150 matched words from the A and B word lists were selected (please see Woodhead et al., 2018, Supplementary Materials, for further details). One list was assigned to be trained and the other to be untrained. These word lists were individualised for each patient. The aims of this word selection process were: to have no significant difference in the patient's baseline reading ability (accuracy or RT) between the selected A and B words; to have no significant difference in psycholinguistic variables (length, frequency, imageability, regularity or N-size) between the selected A and B words; and to have no significant difference in reading ability (accuracy or RT) between the selected word lists and the full list of words tested at baseline. The purpose of this latter aim was to avoid the possibility of regression to the mean, which would have been an issue if we had only selected words for therapy that the participants read poorly at baseline.

At the testing sessions immediately before and after therapy (T3 and T4), participants were tested on a subset of 90 words from each word list (trained items and untrained items; see Woodhead et al., 2018 for further details). Words were presented in a random order over 3 blocks. E-prime software (Schneider et al., 2002) was used to present words in the centre of a screen in black, lower case, size 36 Arial font on a grey background. Participants were instructed to read the words aloud as quickly and accurately as they could into a voice-key microphone. Accuracy was coded online as follows; 1- correct response, 0.5- self corrected errors or verbal false starts, 0- incorrect response. Responses greater than 4 seconds post-stimulus onset were coded as incorrect. Reaction times were excluded for: i) voice-key failures; ii) incorrect and self-corrected responses; and, iii) RTs greater than 2 standard deviations from the subject's mean. To identify voice-key failures, a visual cue was displayed at the bottom left corner of the screen, which informed the experimenter when the microphone had been triggered. Prior to inputting the accuracy of the participant's response, the experimenter coded the validity of the voice key trigger; 1= accurate, 2 =inaccurate voice-key trigger (for example, if the participant said "erm" or a response was not detected by the microphone).

MEG scanning procedures

Scans were acquired using a VSM MegTech Omega 275 MEG scanner with 274 axial gradiometers in software third gradient-mode at a sampling rate of 480Hz. Fiducial markers on the nasion and left and right pre-auricular points were used to determine head location in the scanner. Head movements were minimised by positioning the participant in a comfortable, well supported position and using padding around the participant's head. Recordings from fiducial markers indicated that the average head movement across a run was 9.14mm (SD=8.18mm).

MEG experimental paradigm and stimuli

Participants were seated upright in the scanner. Trained words (n=150), untrained words (n=150), 'false font' symbol strings (n=150, described previously in Woodhead et al., 2013) and common proper names (e.g. "Jenny", "Bob", n=40) were projected onto the screen approximately 50 cm in front of the participant. Each stimulus was presented for 1000ms followed by a crosshair for 2000ms with a total inter stimulus interval of 3000ms. The stimuli were presented lower case Arial font of size 50 (see Figure 3). The stimuli types were evenly distributed in a pseudorandom order across 4 runs and presented using Cogent software (www.vislab.ucl.ac.uk/cogent.php). Participants were instructed to read the words silently. To ensure that participants attended to every trial, they were asked to respond via button press when they read a proper name. These catch trials were removed from the analysis. The false font condition was included to allow comparison with a dataset from healthy control participants, reported elsewhere (Woodhead et al., 2014). The analysis of the false font trials is not reported in the current paper.

MEG pre-processing

The MEG data were pre-processed in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) using Matlab14a (http://uk.mathworks.com/products/matlab/). Pre-processing steps included: high-pass filtering at 1Hz; removal of eye-movement artefact using the Berg method (Berg and Scherg, 1994); epoching in the window -100ms to 500ms; low-pass filtering at 30Hz; and merging the four runs. Artefact detection using a simple threshold at 2500fT was applied, and channels with greater than 20% of trials removed were rejected. This resulted in the removal of, on average, 40 trials (range 0-260 trials) for each participant (out of a total of 600 trials) and a total of 10 instances where channels were removed. Robust averaging across trials was conducted and a 30Hz low-pass filter was applied. Data from the two time points were merged and a single shell Boundary Element Method forward model was applied.

Source localisation

Dipolar source location was carried out with Variational Bayes Equivalent Current Dipole Modelling (VB-ECD (Kiebel et al., 2008a)) which uses a non-linear optimisation algorithm to simultaneously fit a number of dipoles with different prior distributions on their locations and moments, at a single time point. For each participant, the M170 peak was identified in a semi-automated fashion using the average power of all trained and untrained word trials, in a time window 0-300 msec. The sensor data at the subject-specifically identified M170 peak was used for the VB-ECD dipole modelling. The M170 peak was reliably present in all subjects and is known to represent orthographic processing (Tarkiainen, 1999; Marinkovic et al., 2003; Rossion et al., 2003; Pylkkänen and McElree, 2007; Vartiainen et al., 2009; Zweig and Pylkkänen, 2009).

The Bayesian algorithm requires the specification of a prior mean and variance for the location and moment of each dipole. The location priors were the same as reported in Woodhead et al. 2014, which demonstrated that a 6-source model consisting of the left and right occipital regions (OCC; MNI coordinates: ±15 -95 2), ventral occipital temporal regions (vOT; ± 44 -58 -15) and inferior frontal gyrus (IFG; ± 48 28 0) best fit the M170 peak for word reading in healthy controls.

Source solutions were free to move to any location. Therefore, the following restrictions were placed on the VB-ECD outputs: source locations must be 1) within the anatomically defined regions of interest, 2) greater than 2cm from adjacent sources 3) outside of the lesion. The solution with the greatest negative free-energy (i.e. that best fitted the data) that met the above criteria was selected to be used in the DCM estimations.

Dynamic Causal Modelling

We used DCM to investigate the effective connectivity between neuronal sources within the reading network and how connections strengths were modulated in response to iReadMore therapy. For a detail description of the methodology of DCM the reader is directed elsewhere (David et al., 2005; Kiebel et al., 2006, 2007, 2008b; Garrido et al., 2007; Reato et al., 2013).

Essentially, DCM employs a biologically informed neural mass model that uses the characteristic response rates and patterns of connectivity (Felleman and Van Essen, 1991) of three neuronal subpopulations (pyramidal cells, spiny stellate cells and inhibitory interneurons) within the layers of the cortical column (Jansen and Rit, 1995) to model the connections between different sources. For example, forward connections innervate spiny stellate cells in the granular layer which results in an excitatory effect, backward connections synapse pyramidal cells and inhibitory interneurons in the supra- and infra granular layers and hence can be excitatory or inhibitory, lateral connections can innervate all three layers of the cortical column and thus can also have an inhibitory or excitatory influence on the target region.

Self-connections are also modelled within the DCM. These quantify the maximal amplitude of the post-synaptic response in each cell population in that region (Kiebel et al., 2007). These maximal responses are modulated by gain parameters. Gain parameters greater than one increase the maximal response that can be elicited from a neuronal region. As such, the gain parameters are a measure of a region's sensitivity to an input.

iReadMore training improved participants' word reading accuracy for trained items only. The aim of the DCM analysis was to identify connection strengths that were significantly modulated by iReadMore training for these trained words, over and above any test-retest effects observed for untrained items. The data used for the DCM analysis were the evoked responses to trained and untrained words presented before and after therapy (Tr_Before; Un_Before; Tr_After; Un_After). We were interested in how therapy affected the early stages of word processing, so activity in the 0-300 ms time window was modelled. The sensory inputs to the model were specified as entering the left and right OCC. The A matrix modelled the connection strengths for the Tr_Before trials. Two B matrices modelled how connection strengths were modulated by therapy. The first (Matrix B1) estimated the modulation for trained words over time (Tr_Before vs Tr_After). To ensure the modulation observed in Matrix B1 did not represent a simple effect of time, rather than training per-se, Matrix B2 modelled modulation for untrained items after therapy versus to-be-trained items before therapy (Tr_Before vs Un_After). It is worth noting that an alternative analysis could be to compare Un_Before vs Un_After for the B2 matrix, as this would have meant that both B1 and B2 would have compared the same items before versus after training. However, this mis-match of items in B2 is unlikely to have made a significant impact on the results because before training, all items were novel and each patient's to-be-trained and never-trained word lists were matched for baseline performance and psycholinguistic properties.

Similar to other studies (Woodhead et al., 2013, 2014), and in order to reduce the model space to a manageable computational level, we placed the following constraints on how network connections varied between models: i) lateral connections were only allowed within the same level of the cortical hierarchy (i.e. left OCC to right OCC) and not between levels (e.g. left OCC to right vOT); ii) lateral connections were reciprocal (e.g. a connection from the left vOT to right vOT was mirrored by a connection from the right vOT to the left vOT); iii) forward and backward connections were symmetrical between hemispheres. This resulted in nine independently varying connections leading to 512 models (2^9) per subject, all of which were fitted to their individual MEG data.

Bayesian model averaging

Random effects Bayesian Model Averaging (BMA) (Penny et al., 2010) was used to identify the average change in each connection strength across all models and all participants. BMA considers the entire model space and computes weighted averages according to the posterior probability for each model.

Experimental Design and Statistical Analysis

Word reading test analysis

Change in word reading accuracy and RT were calculated over the baseline period and training block for each word list. Change was simply calculated as the difference from one time-point to the next. Repeated-measures ANOVAs were calculated with within-subject factors of Block (pre-training (T3-Baseline) vs training (T4-T3)) and Word-List (Untrained vs Trained).

MEG Analysis: Group-level effects of iReadMore therapy on the reading network

The DCM analysis identified the training-related modulation in effective connectivity between regions at the group level. We defined whether connections showed training-related modulation according to two criteria: i) there was significant modulation in Matrix B1 (Tr_Before vs Tr_After); and ii) the therapy-specific modulation in Matrix B1 was significantly different to the non-specific change over time in Matrix B2 (Tr_Before vs Un_After).

For the first criteria, a non-parametric proportion test was used for each connection to test whether modulation in Matrix B1 (Tr_Before vs Tr_After) was significant. A Gaussian distribution based on the posterior mean and standard deviation was generated for each connection from which 10000 samples were obtained. A connection was deemed to be significantly stronger after therapy if >90% of samples were *greater than* 1; and significantly weaker if >90% of samples were *less than* 1 (Richardson et al., 2011; Seghier, 2013; Woodhead et al., 2013).

To identify therapy specific training effects, rather than a simple effect of time, a second analysis was performed to compare the B1 and B2 matrices. The B1 matrix provides the modulation of connections for training over time (Tr_Before vs Tr_After) whereas the B2 matrix encapsulates the main effect of time in the absence of any training (Tr_Before vs Un_After). If the experiment only induced a simple effect of time, the modulation of the two B matrices would be very similar, and not significantly different from each other. If, on the other hand, there was an additional effect of therapy over time, we would expect the modulation in the two B matrices to be different. Using a fixed-effect within-subject Bayesian Model Comparison (BMC), we compared the two models; i) Matrix B1 $\neq$ Matrix B2; and ii) Matrix B1 = Matrix B2. Log Bayes Factors > 3 indicate that connections in B1 were significantly different to those in B2 (i.e. the effect of therapy could not be simply explained as an effect of time). If both criteria are satisfied then the connection is significantly modulated by reading therapy (criterion 1) and is not simply explained as an effect of time (criterion 2).

Results

Training effects on reading ability

Participants completed on average 33.35 hours (sd=2.65 hours; range: 25.33 to 37.21 hours) of iReadMore therapy over the training period.

A repeated-measures ANOVA revealed a significant Block by Word-List interaction for word reading accuracy ($F(1,22)=11.869$, $P= 0.00231$; see Figure 4). Paired t-tests showed the change in accuracy for trained words was significantly greater during the training block compared to the pre-training block ($t(22)=-3.11$, $P=0.010$), and change over the training block was significantly greater for trained words compared to untrained words ($t(22)=5.89$, $P=0.001$). Change in accuracy for untrained items was not significantly different between Blocks ($t(22)=1.479$, $P=0.153$). This indicates that therapy significantly improved word reading accuracy for trained words only. Word reading accuracy improved by on average 8.4% (SD=7.36; range: -2.77 to 31.66) for trained words compared to -0.11% (SD=5.39; range: -13.33 to 8.36) for untrained words. A repeated-measures ANOVA of word reading reaction time data revealed no significant Block by Word List interaction ($F(1,21)=0.461$, $P=0.505$) and no main effect of Block ($F(1,21)=2.983$, $P=0.099$) or Word-List $F(1,21)=0.066$, $P=0.800$).

MEG scanner task results

Participants successfully completed the within-scanner name detection task. Average accuracy for name trials was 89.71% (SD=16.01) and the average percentage of false alarms (where the button was pressed for a trial other than a name) were 3.91% (SD=6.06).

Cardiac artefacts

In response to a reviewer's comment, we tested whether cardiac artefacts could be confounding our results by carrying out a post-hoc ICA analysis on the raw MEG data. A heartbeat artefact component was identifiable in n=18 out of 23 participants. This component was epoched according to trial onset times for the four main conditions. The 'cardiac ERP' data was averaged into 10ms time bins over the 0-300ms time window (giving 30 time bins). A 2x2 repeated measures ANOVA at each time point with factors Time (before vs after training) and Wordlist (trained vs untrained words) revealed no significant main effect of either Time or Wordlist in any of these 30 time bins.

Cardiac artefacts may have also added unsystematic noise to the data. This noise was however not related to the trial type or time from trial onset. All DCM analyses were based on averaged data (typically 150 trials) which would have significantly attenuated this confound. Additionally, we used a robust averaging procedure, which uses an iterative process to place weights on within trial samples of data based on the degree of artefact present within the trial (Leski, 2002; Litvak et al., 2011). When the data is averaged across trials, these weightings serve to down-weight outliers.

We conclude that any cardiac artefacts were unlikely to have influenced our DCM results, due to their random occurrence with respect to both stimulus onset and stimulus type allied with the use of robust averaging to minimise any effect that they may have had on the data.

Source Localisation

The average latency of the M170 peak was 189.71ms (range: 156.67 – 215.00) and the average peak amplitude was 37.15fT (range: 14.46-63.8fT). To show that the M170 peak is related to orthographic processing a correlation was performed between baseline word reading accuracy and M170 latency and amplitude. This revealed a significant negative correlation $r=-0.550$, $P=0.007$ indicating that those patients with greater word reading accuracy had earlier M170 peaks. See Figure 2A for each participants' dipole location plotted on a glass brain.

MEG Analysis: Group-level effects of iReadMore therapy on the reading network

Table 2 displays the posterior mean and exceedance probability for connections that showed significant therapy effects; i.e. that were significantly modulated in Matrix B1 (Tr_Before vs Tr_After) but this modulation was significantly different to that in Matrix B2 (Un_Before vs Tr_After). Eight connections were significantly stronger after therapy than before, and five were significantly weaker (see Figure 5).

Stronger connections for trained words after therapy

Of the eight connections significantly strengthened by iReadMore training two were feedforward connections in the left hemisphere, two were lateral (between hemisphere) connections from right to left and four were self-connections. More specifically they were: the feedforward connections from left OCC to left IFG and left vOT; the lateral connections between the OCCs and IFGs in the right to left direction; the self-connections in left and right OCCs and IFGs (bottom and top of the reading hierarchy respectively). Self-connections indicate the sensitivity of a region to an input; indicating that these regions became more sensitive to trained words with therapy.

Weaker connections for trained words after therapy

Of the five connections significantly weakened by iReadMore training, three were feedback connections, two lateral and one was a self-connection. More specifically they were: the feedback connections from both IFGs to both vOTs and from left vOT to left OCC; the lateral connection between the OCCs in the left to right direction; the self-connection on the right vOT.

Discussion

Our analysis explored training-induced connectivity modulation within the reading network of stroke patients with CA at the group level. We observed changes distributed across the reading network. We identified increased regional sensitivity to trained words (changes in regions' self-connections) bilaterally at the top (frontal regions) and bottom (occipital regions) of the reading network. As expected, this included the left IFG. The between-region connections modified by therapy were predominately in the left hemisphere or, when interhemispheric, were from right to left. Contrary to our predictions, stronger connections were observed in a feedforward direction from left OCC to vOT and from left vOT to IFG. Together, these findings indicate that iReadMore training predominantly alters left hemisphere connectivity and increases the influence of bottom-up processes.

The therapy induced inter-regional modulation of connectivity was predominantly in a feedforward direction. Stronger connections were observed between the left OCC and left IFG and left OCC and left vOT. These connections were also stronger for words compared to false fonts in the first 300ms of reading in a group of healthy control participants (Woodhead et al., 2014). According to the Local Combination Detector (LCD) model (Dehaene et al., 2005; Dehaene and Cohen, 2011) neurons are tuned to progressively larger fragments of the word as their location moves along the ventral pathway. It is possible that mass exposure to the orthographic stimuli enhanced the processing of word forms within the ventral reading route. These results, when viewed with the reduced strength of feedback connections from the left IFG to left vOT and from left vOT to left OCC, suggests that iReadMore training in these patients modulates lower-order visual representations, as opposed to higher-order, more abstract ones, in order to improve word reading accuracy.

This finding is in contrast to patients with Pure Alexia (PA), where iReadMore training effects were driven by increased feedback from the left IFG to left OCC (Woodhead et al., 2013). It was suggested that improved predictions from the phonological and semantic representations within the IFG constrained the visual processing of trained words. This discrepancy may reflect differences in the lesion location in the two groups; with damage to the PCA territory in PA patients and the MCA territory in CA patients (see Figure 2B). In response to therapy, each group may have maximised their available intact resources. Therapy effects in PA patients are likely to rely on improving feedback support from the intact phonological and semantic representation of words within their left IFG as damage affects input to the reading network. Increased IFG involvement has been identified for task demanding subordinate levels of semantic knowledge (Nagel et al., 2008; Whitney et al., 2011) and tasks relating to phonology (Devlin et al., 2003; Drakesmith et al., 2015). By contrast, CA patients have damage to the central phonological and/or semantic representations (or connections to them; Crisp and Lambon Ralph, 2006; Robson et al., 2011; Hoffman et al., 2015). Therefore, therapy may increase reliance on orthographic processing to drive rebuilding or reconnecting of the phonological and/or semantic representations in a feedforward manner.

Increases in self-connection strengths were observed in the left and right OCCs and IFGs. In DCM, self-connections act as a gain control (Kiebel et al., 2007). The left IFG has been implicated the early stages of visual word recognition (Cornelissen et al., 2009; Wheat et al., 2010; Woodhead et al., 2014) and was modulated by iReadMore therapy in patients with PA (Woodhead et al., 2013); however, we did not expect the self-connection of the right IFG in our CA patients to also became stronger. Support from the right IFG in language tasks has been reported in aphasia rehabilitation research (Crinion and Price, 2005; Naeser et al., 2011; Turkeltaub et al., 2012; Mohr et al., 2016; Nardo et al., 2017). However, it has been argued that this strategy may be ineffective in comparison to using perilesional left hemisphere regions (Heiss and Thiel, 2006). The stronger self-connections in both IFGs may reflect the differences in patients' progress with training. In a participant with phonological dyslexia, increased right IFG activity was observed immediately following training. However, when training continued on words read correctly immediately post-therapy, increased activation was observed in left hemisphere perilesional regions (Kurland et al., 2008). It has been suggested that the right IFG has a role in assisting with error monitoring and attention control (Hampshire et al., 2010). The increased connection strength from right IFG to left IFG may suggest that the right IFG has a different role in word reading, potentially related to error monitoring, which will have also been modulated by iReadMore.

Within the right hemisphere, the connection from right IFG to right vOT became weaker with training, as did the right vOT self-connection. This further suggests a reduced role of the right hemisphere in reading after iReadMore training.

iReadMore was designed to retrain word reading across all subtypes of CA through repeated activation of the semantic, phonological and orthographic representations of trained words (Woodhead et al., 2018). Retraining in this omnibus manner potentially strengthened the mappings between differing cortical representations of words. It should be noted that almost all participants were classified as having either phonological or deep dyslexia (indicating a deficit in the phonological domain or sublexical reading route), which may limit our interpretations to this patient group. However, in practice we observe that few patients have ‘pure’ deficits of one type or another (Leff & Starrfelt, 2013), and it is an open question to what extent reading rehabilitation targets one reading route over the other. In line with previous research (Abel et al., 2015; Rueckl et al., 2015), our study suggests that therapeutic effects play out among both surviving left and right hemisphere regions, albeit with a leftward bias.

The following connections became stronger with training: a) the right OCC self-connection; and, b) the connection from right to left OCC. This may reflect selective tuning of visual cortex to the orthographic information in trained words induced by multiple, repetitive exposure with trial-by-trial feedback. According to the split fovea theory, visual information from the front of a word is received by the right OCC as the optimal viewing position is usually just to the left of centre of any given word (Nazir et al., 1992). Acceptable dipole locations were not restricted to V1 so extra-striate regions will almost certainly have contributed to the observed effects. As hemifield integration occurs above the level of V1, the changes in the right OCC self-connection and interhemispheric connection to left OCC suggests increased sensitivity to the front part (left of fixation) of trained words (Perea and Lupker, 2003). This is consistent with the LCD reading model (Dehaene et al., 2001; Cohen et al., 2002; Perea and Lupker, 2003).

In summary, in a group of patients with CA (mainly with either phonological or deep dyslexia), improved word reading after iReadMore training was associated with distributed changes across the residual reading network. We identified a mixture of: a) within hemisphere connections (mainly left-lateralized and feedforward), that were strengthened by therapy; b) bihemispheric connections (particularly self-connections at both the top and bottom of the reading hierarchy); c) between hemisphere connections (right to left pattern). The iReadMore therapy app will be available to the public in 2018 (http://www.ucl.ac.uk/aphasialab/apps/ireadmore.html).

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Table 1. Demographic and clinical information on each patient. Reading change (%) for trained items was calculated by subtracting pre-training (T3) WRT accuracy (as a raw per cent) from post-training accuracy (T4) for trained words only. CA= central alexia; P= phonological alexia; S= surface alexia; D= deep alexia.

Table 2. Results of the DCM analysis (group-level effects of iReadMore therapy on the reading network). Posterior means and exceedance probabilities from Matrix B1 (Tr_Before vs Tr_After) for the 13 connections that were shown to be significantly modulated by iReadMore therapy. L/ROCC= left/right occipital; L/RvOT=left/right ventral occipitotemporal cortex; L/RIFG= left/right Inferior Frontal Gyrus.

Figure 1. Study design. The Baseline assessment took place over two testing sessions 1-2 weeks apart (T1 and T2). An MEG scan and behavioural assessment was conducted before (T3) and after (T4) a four week block of iReadMore training.

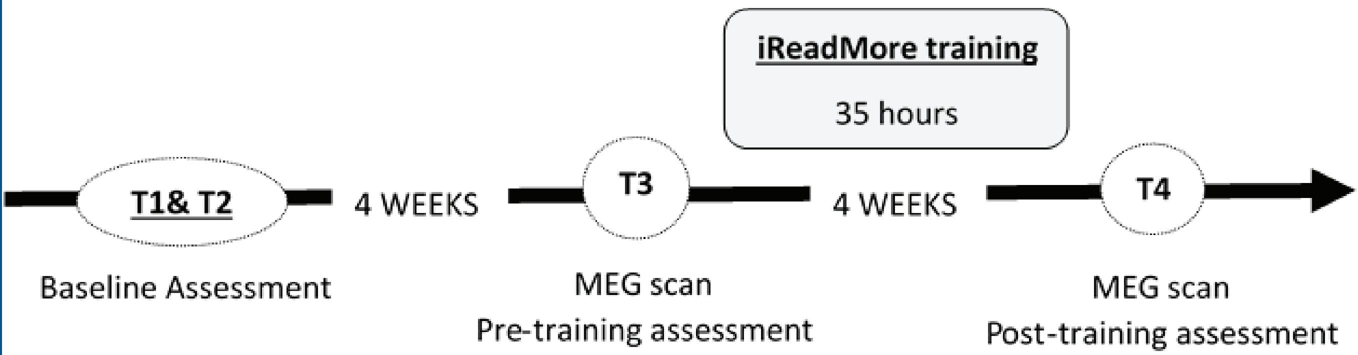
Figure 2. A) Optimal source locations identified using Variational Bayesian equivalent current dipole modelling for each subject, plotted on a glass brain in MNI space. Average dipole location across the group are given for the six sources; occipital (blue), ventral occipital temporal (grey) and inferior frontal gyrus (red). B) Lesion overlay map for the group (n=23) where hotter colours indicate greater number of patients with lesions affecting that area.

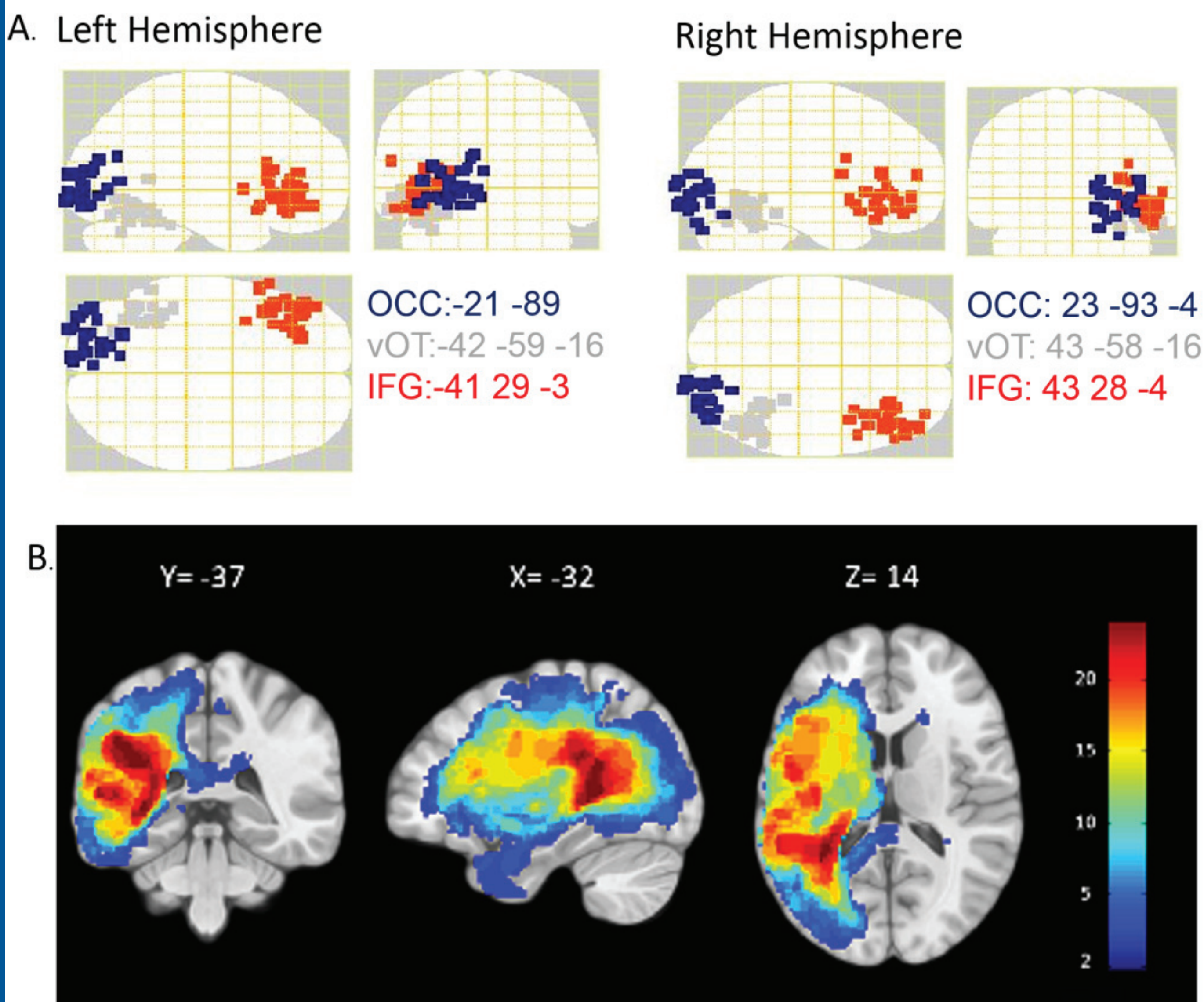
Figure 3. Stimulus presentation procedure for the MEG scans. Participants were scanned before and after training. At each session, there were 150 trials for each condition of interest (Trained and Untrained words), 150 trials for false fonts (omitted from this analysis) and 40 catch trials (names).

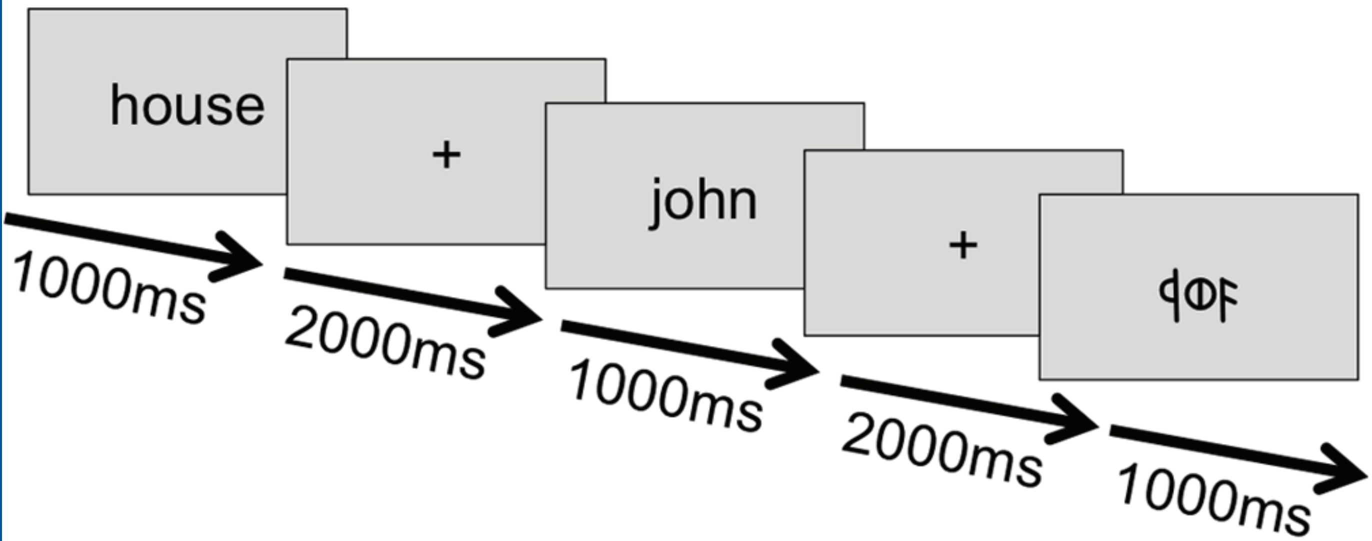
Figure 4. Change over time in (A) mean word reading accuracy (n=23) and (B) reaction times (n=22) for trained words (blue) and untrained words (red). Error bars indicate 95% confidence intervals.

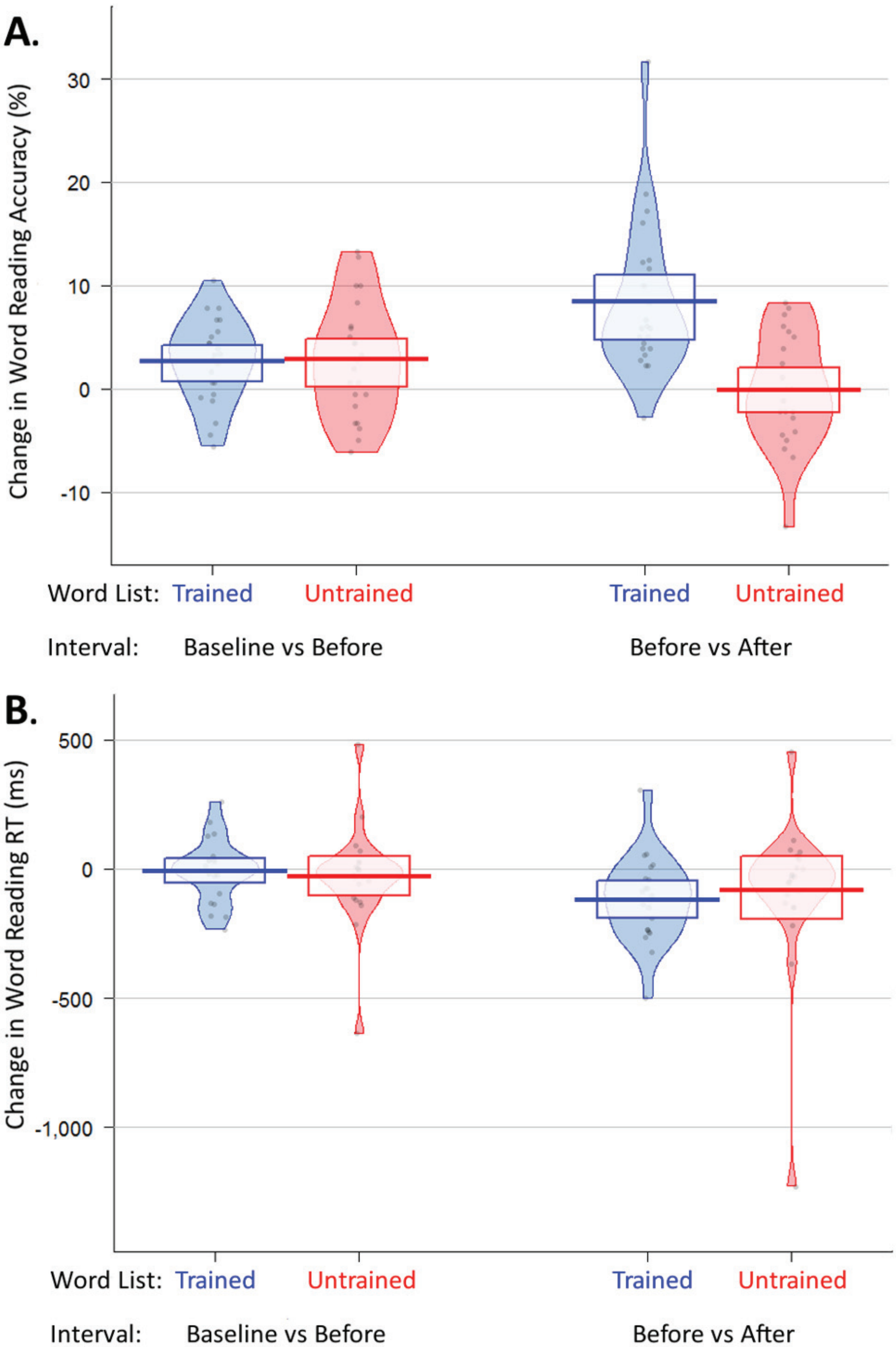
Figure 5. Results of the DCM analysis: Modulated connection strengths for words trained with iReadMore after training. These are connections that met the following criteria; i) there was significant modulation in Matrix B1 (Tr_Before vs Tr_After); and ii) the therapy-specific modulation in Matrix B1 was significantly different to the non-specific change over time in Matrix B2 (Tr_Before vs Un_After). Connections in red

became significantly stronger after training, whereas connections in blue because significantly weaker after training.

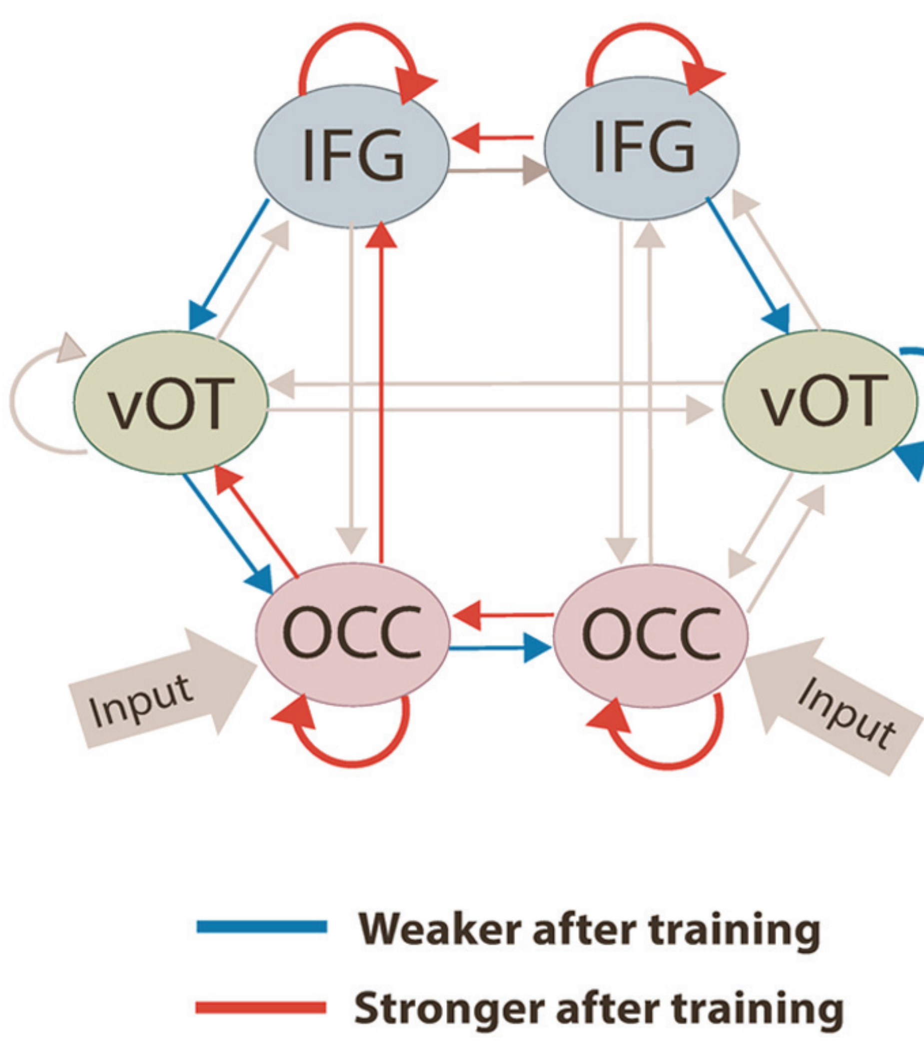

iReadMore training
35 hours
T1& T2
4 WEEKS
T3
4 WEEKS
T4
Baseline Assessment
MEG scan
Pre-training assessment
MEG scan
Post-training assessment


A.
Left Hemisphere
Right Hemisphere
OCC:-21 -89
vOT:-42 -59 -16
IFG:-41 29 -3
OCC: 23 -93 -4
vOT: 43 -58 -16
IFG: 43 28 -4
B.
Y= -37
X= -32
Z= 14
20
15
10
5
2


house
+
john
+
1000ms
2000ms
1000ms
2000ms
1000ms


A.
Change in Word Reading Accuracy (%)
30
20
10
0
-10
Word List: Trained Untrained Trained Untrained
Interval: Baseline vs Before Before vs After
B.
Change in Word Reading RT (ms)
500
0
-500
-1,000
Word List: Trained Untrained Trained Untrained
Interval: Baseline vs Before Before vs After

Group-level effects of iReadMore therapy on the reading network



ID	Age (years)	Gender	Time post-stroke (months)	Lesion Volume (cm³)	CA subtype	CAT naming, (%)	Pseudo-word Reading (%)	Baseline Word Reading (%)	Reading change (%) for trained items
P01	44	Male	94	240.9	D	69	0	58.4	31.7
P02	50	Male	82	304.5	D	53	0	40.3	17.2
P03	64	Male	25	102.7	P	81	70	96.7	-2.8
P04	52	Male	66	122.7	P	66	0	71.1	18.9
P05	56	Female	93	149.8	S	5	75	63.8	8.3
P06	55	Female	75	151.2	P	93	30	91.9	3.9
P07	33	Female	59	181	P	95	2.5	90.1	2.8
P08	67	Male	107	11.7	D	72	2.5	12.5	12.5
P09	43	Female	55	399.2	D	81	0	58.2	11.7
P10	61	Male	19	195.6	D	40	0	3.4	5.0
P11	52	Male	12	31.2	P	88	75	96.3	3.9
P12	50	Female	14	59.4	P	83	25	90.6	2.2
P13	54	Male	24	149.3	P	86	65	91.5	4.4
P14	56	Male	23	45.1	P	72	0	80.3	3.3
P15	54	Male	39	189.7	P	14	2.5	47.3	6.1
P16	73	Male	158	205.2	D	71	0	20.0	5.8
P17	60	Male	16	102.6	D	33	10	28.1	10.0
P18	78	Male	22	128.5	P	43	7.5	75.4	2.2
P19	50	Female	72	141.3	P	28	5	35.9	5.0
P20	72	Male	101	243.3	D	9	0	13.4	5.8
P21	58	Female	41	297.7	P	81	0	59.5	16.1
P22	42	Male	13	43.7	P	72	27.5	74.9	12.2
P23	26	Female	81	161.9	D	79	0	75.5	6.7

Connection	Posterior mean	Exceedance Probability
Stronger with training		
LOCC to LOCC	1.02	1.00
LOCC to LvOT	1.17	1.00
LOCC to LIFG	1.16	1.00
ROCC to LOCC	1.07	0.97
ROCC to ROCC	1.07	1.00
LIFG to LIFG	1.10	1.00
RIFG to LIFG	1.08	0.96
RIFG to RIFG	1.03	0.99
Weaker with training		
LOCC to ROCC	0.86	0.00
LvOT to LOCC	0.92	0.01
RvOT to RvOT	0.97	0.01
LIFG to LvOT	0.80	0.00
RIFG to RvOT	0.91	0.00

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