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

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1 Title (50 words max): How does iReadMore therapy change the reading network of
2 patients with central alexia?

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

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33

34 **Abstract**

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

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

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

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

57 **Significance Statement**

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

69 **Introduction**

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

81

82 After left hemisphere stroke, the role of spared ipsilesional regions and right
83 hemisphere homologues in supporting aphasia recovery are unclear (Adair et al.,
84 2000; Tsapkini et al., 2011; Crinion and Leff, 2015; Hartwigsen and Saur, 2017).

85 There is evidence for functional reorganisation in spared left hemisphere regions
86 (Jobard et al., 2003; Fridriksson, 2010; Abel et al., 2014, 2015; van Hees et al.,
87 2014; Bonilha et al., 2016; Pillay et al., 2017); while other studies have identified
88 right hemisphere homologues fulfilling this function (Meinzer et al., 2006; Richter et
89 al., 2008; Lee et al., 2017) both accounts may be correct and aphasia recovery may
90 rely on a combination of mechanisms (Saur et al., 2006; Kurland et al., 2008;
91 Turkeltaub et al., 2011; Crinion and Leff, 2015; Mohr et al., 2016). We modelled a
92 bilateral reading network in patients with CA to ascertain the effects of therapy within
93 and between the hemispheres.

94 While post-stroke aphasia is the result of focal damage, it is increasingly viewed as a
95 network disorder (Hartwigsen and Saur, 2017). Neuroimaging studies of skilled
96 readers show that word reading activates a predominantly left-lateralised network of
97 occipitotemporal, temporal and inferior frontal areas (Heim et al., 2005; Graves et al.,
98 2010; Price, 2012; Carreiras et al., 2014; Hoffman et al., 2015; Perrone-Bertolotti et
99 al., 2017; Xu et al., 2017; Zhou and Shu, 2017). The local combination detector
100 (LCD) model of visual word recognition suggests that because neurons are tuned to
101 progressively larger fragments of a word as their location moves anteriorly, word
102 reading is achieved primarily through feed-forward processing along the visual
103 ventral stream (Dehaene et al., 2005). However, an alternative account suggests
104 that efficient word recognition relies on interactive feedforward (bottom-up) and
105 feedback (top-down) processing within this network (Cornelissen et al., 2009; Wheat

106 et al., 2010; Price and Devlin, 2011; Woodhead et al., 2014). Dynamic causal
107 modelling (DMC) identifies the causal influence of one region upon another, allowing
108 us to explore the interaction between top-down and bottom-up processes.

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

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

128

129 **Method**

130 Study design

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

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

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

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

147 Participants

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

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

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

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

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

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

176 Structural MRI

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

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

193 iReadMore training

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

202 revealed the written word, spoken word and a picture of the word (all congruent with
203 each other).

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

213 Training stimuli

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

218 Over two baseline sessions (T1 and T2), CA participants completed an assessment
219 of the entire word corpus whereby they read each word out aloud. Based on each
220 participant's baseline performance (word reading accuracy and speed), a
221 customised set of 150 matched words from the A and B word lists were selected
222 (please see Woodhead et al., 2018, Supplementary Materials, for further details).

223 One list was assigned to be trained and the other to be untrained. These word lists
224 were individualised for each patient. The aims of this word selection process were: to
225 have no significant difference in the patient's baseline reading ability (accuracy or
226 RT) between the selected A and B words; to have no significant difference in

227 psycholinguistic variables (length, frequency, imageability, regularity or N-size)
228 between the selected A and B words; and to have no significant difference in reading
229 ability (accuracy or RT) between the selected word lists and the full list of words
230 tested at baseline. The purpose of this latter aim was to avoid the possibility of
231 regression to the mean, which would have been an issue if we had only selected
232 words for therapy that the participants read poorly at baseline.

233 At the testing sessions immediately before and after therapy (T3 and T4),
234 participants were tested on a subset of 90 words from each word list (trained items
235 and untrained items; see Woodhead et al., 2018 for further details). Words were
236 presented in a random order over 3 blocks. E-prime software (Schneider et al., 2002)
237 was used to present words in the centre of a screen in black, lower case, size 36
238 Arial font on a grey background. Participants were instructed to read the words aloud
239 as quickly and accurately as they could into a voice-key microphone. Accuracy was
240 coded online as follows; 1- correct response, 0.5- self corrected errors or verbal false
241 starts, 0- incorrect response. Responses greater than 4 seconds post-stimulus onset
242 were coded as incorrect. Reaction times were excluded for: i) voice-key failures; ii)
243 incorrect and self-corrected responses; and, iii) RTs greater than 2 standard
244 deviations from the subject's mean. To identify voice-key failures, a visual cue was
245 displayed at the bottom left corner of the screen, which informed the experimenter
246 when the microphone had been triggered. Prior to inputting the accuracy of the
247 participant's response, the experimenter coded the validity of the voice key trigger;
248 1= accurate, 2 =inaccurate voice-key trigger (for example, if the participant said
249 "erm" or a response was not detected by the microphone).

250 MEG scanning procedures

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

258 MEG experimental paradigm and stimuli

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

274 MEG pre-processing

275 The MEG data were pre-processed in SPM12
276 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) using Matlab14a
277 (<http://uk.mathworks.com/products/matlab/>). Pre-processing steps included: high-
278 pass filtering at 1Hz; removal of eye-movement artefact using the Berg method (Berg
279 and Scherg, 1994); epoching in the window -100ms to 500ms; low-pass filtering at
280 30Hz; and merging the four runs. Artefact detection using a simple threshold at
281 2500fT was applied, and channels with greater than 20% of trials removed were
282 rejected. This resulted in the removal of, on average, 40 trials (range 0-260 trials) for
283 each participant (out of a total of 600 trials) and a total of 10 instances where
284 channels were removed. Robust averaging across trials was conducted and a 30Hz
285 low-pass filter was applied. Data from the two time points were merged and a single
286 shell Boundary Element Method forward model was applied.

287 Source localisation

288 Dipolar source location was carried out with Variational Bayes Equivalent Current
289 Dipole Modelling (VB-ECD (Kiebel et al., 2008a)) which uses a non-linear
290 optimisation algorithm to simultaneously fit a number of dipoles with different prior
291 distributions on their locations and moments, at a single time point. For each
292 participant, the M170 peak was identified in a semi-automated fashion using the
293 average power of all trained and untrained word trials, in a time window 0-300 msec.
294 The sensor data at the subject-specifically identified M170 peak was used for the
295 VB-ECD dipole modelling. The M170 peak was reliably present in all subjects and is
296 known to represent orthographic processing (Tarkiainen, 1999; Marinkovic et al.,
297 2003; Rossion et al., 2003; Pylkkänen and McElree, 2007; Vartiainen et al., 2009;
298 Zweig and Pylkkänen, 2009).

299 The Bayesian algorithm requires the specification of a prior mean and variance for
300 the location and moment of each dipole. The location priors were the same as
301 reported in Woodhead et al. 2014, which demonstrated that a 6-source model
302 consisting of the left and right occipital regions (OCC; MNI coordinates: ± 15 -95 2),
303 ventral occipital temporal regions (vOT; ± 44 -58 -15) and inferior frontal gyrus (IFG;
304 ± 48 28 0) best fit the M170 peak for word reading in healthy controls.

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

311 Dynamic Causal Modelling

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

317 Essentially, DCM employs a biologically informed neural mass model that uses the
318 characteristic response rates and patterns of connectivity (Felleman and Van Essen,
319 1991) of three neuronal subpopulations (pyramidal cells, spiny stellate cells and
320 inhibitory interneurons) within the layers of the cortical column (Jansen and Rit,
321 1995) to model the connections between different sources. For example, forward
322 connections innervate spiny stellate cells in the granular layer which results in an
323 excitatory effect, backward connections synapse pyramidal cells and inhibitory

324 interneurons in the supra- and infra granular layers and hence can be excitatory or
325 inhibitory, lateral connections can innervate all three layers of the cortical column
326 and thus can also have an inhibitory or excitatory influence on the target region.

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

333 iReadMore training improved participants' word reading accuracy for trained items
334 only. The aim of the DCM analysis was to identify connection strengths that were
335 significantly modulated by iReadMore training for these trained words, over and
336 above any test-retest effects observed for untrained items. The data used for the
337 DCM analysis were the evoked responses to trained and untrained words presented
338 before and after therapy (Tr_Before; Un_Before; Tr_After; Un_After). We were
339 interested in how therapy affected the early stages of word processing, so activity in
340 the 0-300 ms time window was modelled. The sensory inputs to the model were
341 specified as entering the left and right OCC. The A matrix modelled the connection
342 strengths for the Tr_Before trials. Two B matrices modelled how connection
343 strengths were modulated by therapy. The first (Matrix B1) estimated the modulation
344 for trained words over time (Tr_Before vs Tr_After). To ensure the modulation
345 observed in Matrix B1 did not represent a simple effect of time, rather than training
346 per-se, Matrix B2 modelled modulation for untrained items after therapy versus to-
347 be-trained items before therapy (Tr_Before vs Un_After). It is worth noting that an
348 alternative analysis could be to compare Un_Before vs Un_After for the B2 matrix,

349 as this would have meant that both B1 and B2 would have compared the same items
350 before versus after training. However, this mis-match of items in B2 is unlikely to
351 have made a significant impact on the results because before training, all items were
352 novel and each patient's to-be-trained and never-trained word lists were matched for
353 baseline performance and psycholinguistic properties.

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

364 Bayesian model averaging

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

369 Experimental Design and Statistical Analysis

370 Word reading test analysis

371 Change in word reading accuracy and RT were calculated over the baseline period
372 and training block for each word list. Change was simply calculated as the

373 difference from one time-point to the next. Repeated-measures ANOVAs were
374 calculated with within-subject factors of Block (pre-training (T3-Baseline) vs training
375 (T4-T3)) and Word-List (Untrained vs Trained).

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

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

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

391 To identify therapy specific training effects, rather than a simple effect of time, a
392 second analysis was performed to compare the B1 and B2 matrices. The B1 matrix
393 provides the modulation of connections for training over time (Tr_Before vs Tr_After)
394 whereas the B2 matrix encapsulates the main effect of time in the absence of any
395 training (Tr_Before vs Un_After). If the experiment only induced a simple effect of
396 time, the modulation of the two B matrices would be very similar, and not significantly
397 different from each other. If, on the other hand, there was an additional effect of

398 therapy over time, we would expect the modulation in the two B matrices to be
399 different. Using a fixed-effect within-subject Bayesian Model Comparison (BMC), we
400 compared the two models; i) Matrix B1 \neq Matrix B2; and ii) Matrix B1 = Matrix B2.
401 Log Bayes Factors > 3 indicate that connections in B1 were significantly different to
402 those in B2 (i.e. the effect of therapy could not be simply explained as an effect of
403 time). If both criteria are satisfied then the connection is significantly modulated by
404 reading therapy (criterion 1) and is not simply explained as an effect of time (criterion
405 2).

406

407 **Results**

408 Training effects on reading ability

409 Participants completed on average 33.35 hours (sd=2.65 hours; range: 25.33 to
410 37.21 hours) of iReadMore therapy over the training period.

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

422 significant Block by Word List interaction ($F(1,21)=0.461$, $P=0.505$) and no main
423 effect of Block ($F(1,21)=2.983$, $P=0.099$) or Word-List ($F(1,21)=0.066$, $P=0.800$).

424 MEG scanner task results

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

429 Cardiac artefacts

430 In response to a reviewer's comment, we tested whether cardiac artefacts could be
431 confounding our results by carrying out a post-hoc ICA analysis on the raw MEG
432 data. A heartbeat artefact component was identifiable in $n=18$ out of 23 participants.
433 This component was epoched according to trial onset times for the four main
434 conditions. The 'cardiac ERP' data was averaged into 10ms time bins over the 0-
435 300ms time window (giving 30 time bins). A 2x2 repeated measures ANOVA at each
436 time point with factors Time (before vs after training) and Wordlist (trained vs
437 untrained words) revealed no significant main effect of either Time or Wordlist in any
438 of these 30 time bins.

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

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

450 Source Localisation

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

458 MEG Analysis: Group-level effects of iReadMore therapy on the reading 459 network

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

465 *Stronger connections for trained words after therapy*

466 Of the eight connections significantly strengthened by iReadMore training two were
467 feedforward connections in the left hemisphere, two were lateral (between
468 hemisphere) connections from right to left and four were self-connections. More
469 specifically they were: the feedforward connections from left OCC to left IFG and left

470 vOT; the lateral connections between the OCCs and IFGs in the right to left direction;
471 the self-connections in left and right OCCs and IFGs (bottom and top of the reading
472 hierarchy respectively). Self-connections indicate the sensitivity of a region to an
473 input; indicating that these regions became more sensitive to trained words with
474 therapy.

475 Weaker connections for trained words after therapy

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

481 **Discussion**

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

493

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

507

508 This finding is in contrast to patients with Pure Alexia (PA), where iReadMore
509 training effects were driven by increased feedback from the left IFG to left OCC
510 (Woodhead et al., 2013). It was suggested that improved predictions from the
511 phonological and semantic representations within the IFG constrained the visual
512 processing of trained words. This discrepancy may reflect differences in the lesion
513 location in the two groups; with damage to the PCA territory in PA patients and the
514 MCA territory in CA patients (see Figure 2B). In response to therapy, each group
515 may have maximised their available intact resources. Therapy effects in PA patients
516 are likely to rely on improving feedback support from the intact phonological and
517 semantic representation of words within their left IFG as damage affects input to the
518 reading network. Increased IFG involvement has been identified for task demanding

519 subordinate levels of semantic knowledge (Nagel et al., 2008; Whitney et al., 2011)
520 and tasks relating to phonology (Devlin et al., 2003; Drakesmith et al., 2015). By
521 contrast, CA patients have damage to the central phonological and/or semantic
522 representations (or connections to them; Crisp and Lambon Ralph, 2006; Robson et
523 al., 2011; Hoffman et al., 2015). Therefore, therapy may increase reliance on
524 orthographic processing to drive rebuilding or reconnecting of the phonological
525 and/or semantic representations in a feedforward manner.

526

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

544 2010). The increased connection strength from right IFG to left IFG may suggest
545 that the right IFG has a different role in word reading, potentially related to error
546 monitoring, which will have also been modulated by iReadMore.

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

550

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

564

565 The following connections became stronger with training: a) the right OCC self-
566 connection; and, b) the connection from right to left OCC. This may reflect selective
567 tuning of visual cortex to the orthographic information in trained words induced by
568 multiple, repetitive exposure with trial-by-trial feedback. According to the split fovea

569 theory, visual information from the front of a word is received by the right OCC as the
570 optimal viewing position is usually just to the left of centre of any given word (Nazir et
571 al., 1992). Acceptable dipole locations were not restricted to V1 so extra-striate
572 regions will almost certainly have contributed to the observed effects. As hemifield
573 integration occurs above the level of V1, the changes in the right OCC self-
574 connection and interhemispheric connection to left OCC suggests increased
575 sensitivity to the front part (left of fixation) of trained words (Perea and Lupker, 2003).
576 This is consistent with the LCD reading model (Dehaene et al., 2001; Cohen et al.,
577 2002; Perea and Lupker, 2003).

578

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

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953 <http://www.tandfonline.com/doi/abs/10.1080/01690960802180420> [Accessed
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955 Table 1. Demographic and clinical information on each patient. Reading change (%)
956 for trained items was calculated by subtracting pre-training (T3) WRT accuracy (as a
957 raw per cent) from post-training accuracy (T4) for trained words only. CA= central
958 alexia; P= phonological alexia; S= surface alexia; D= deep alexia.

959

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

965

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

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

975

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

980

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

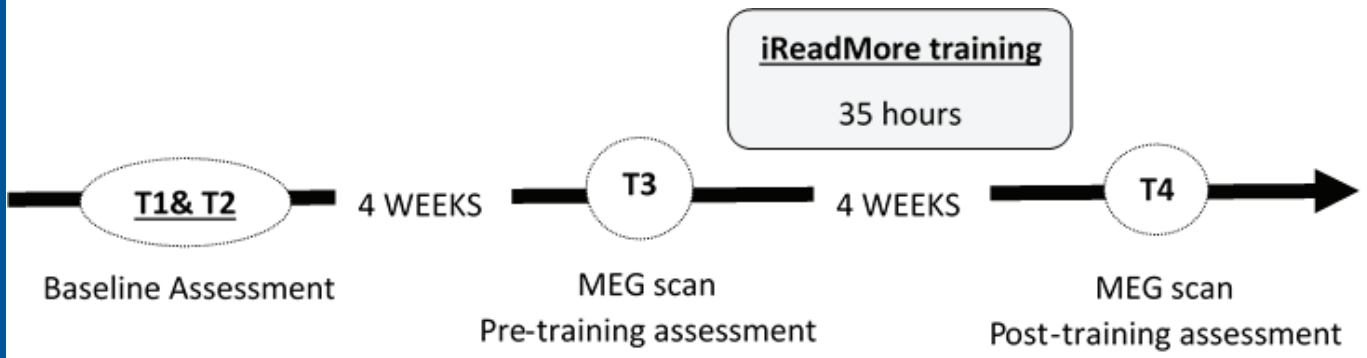
984

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

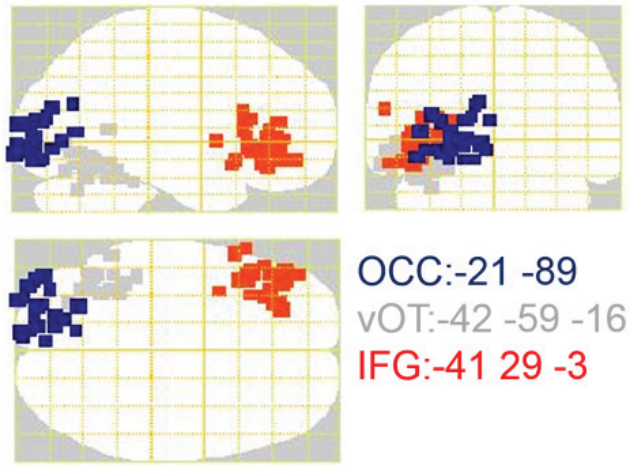
990 became significantly stronger after training, whereas connections in blue because

991 significantly weaker after training.

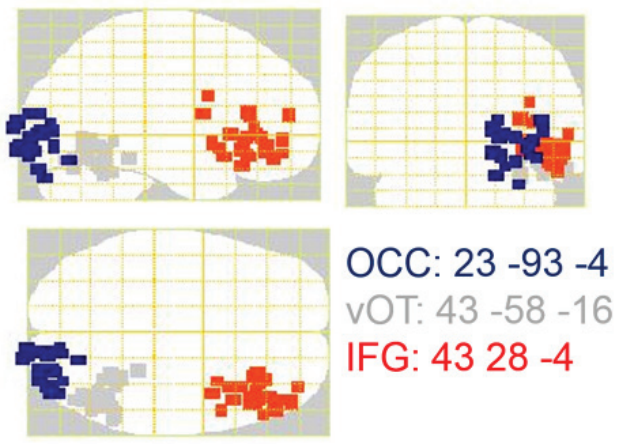
992



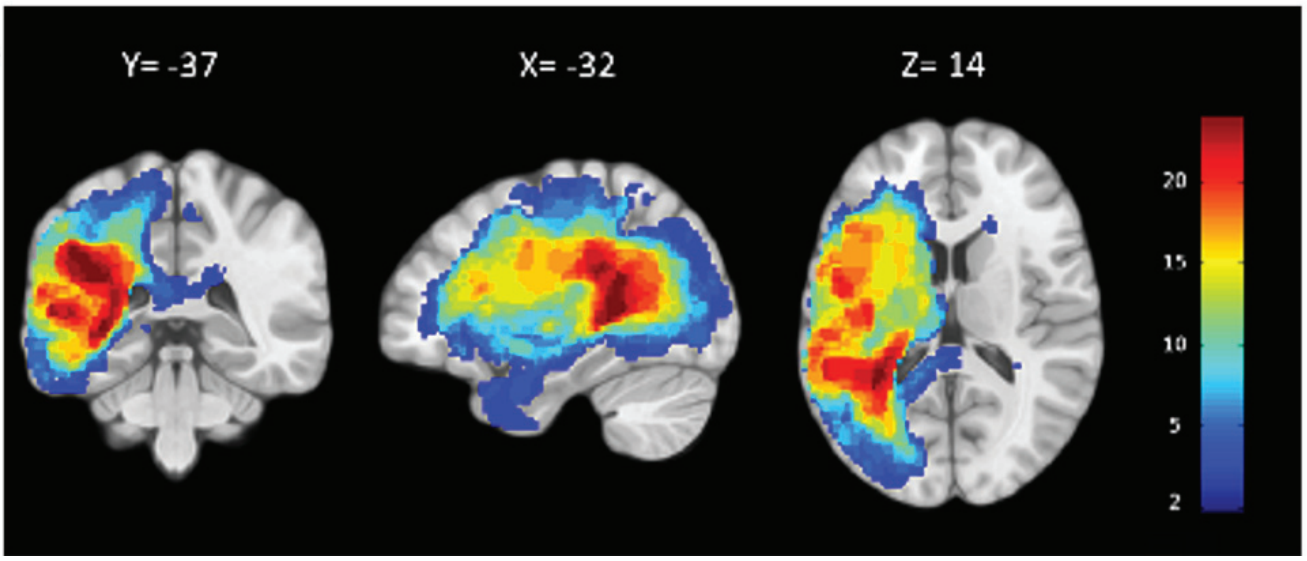
A. Left Hemisphere

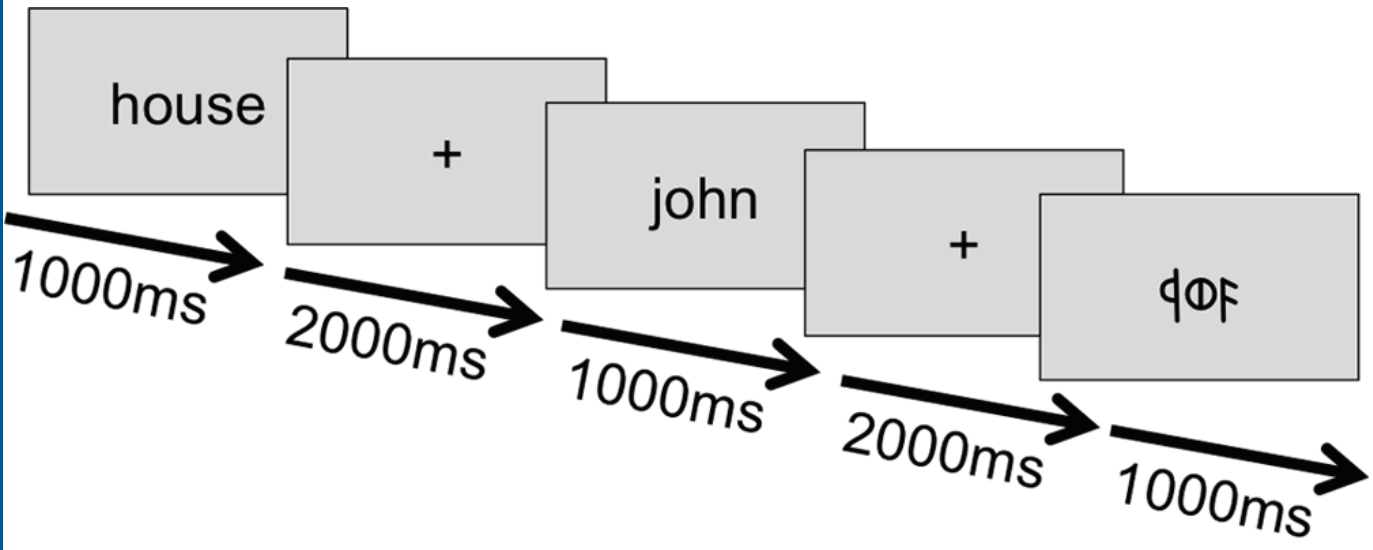


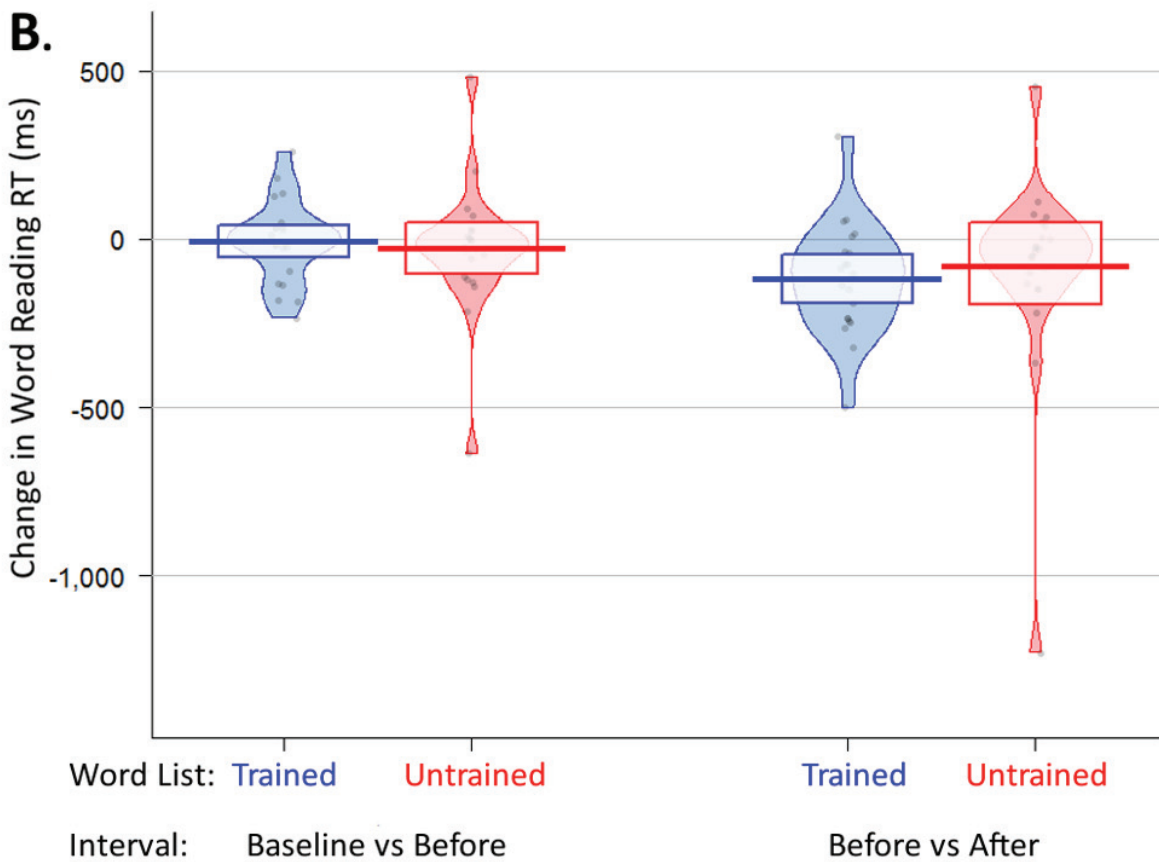
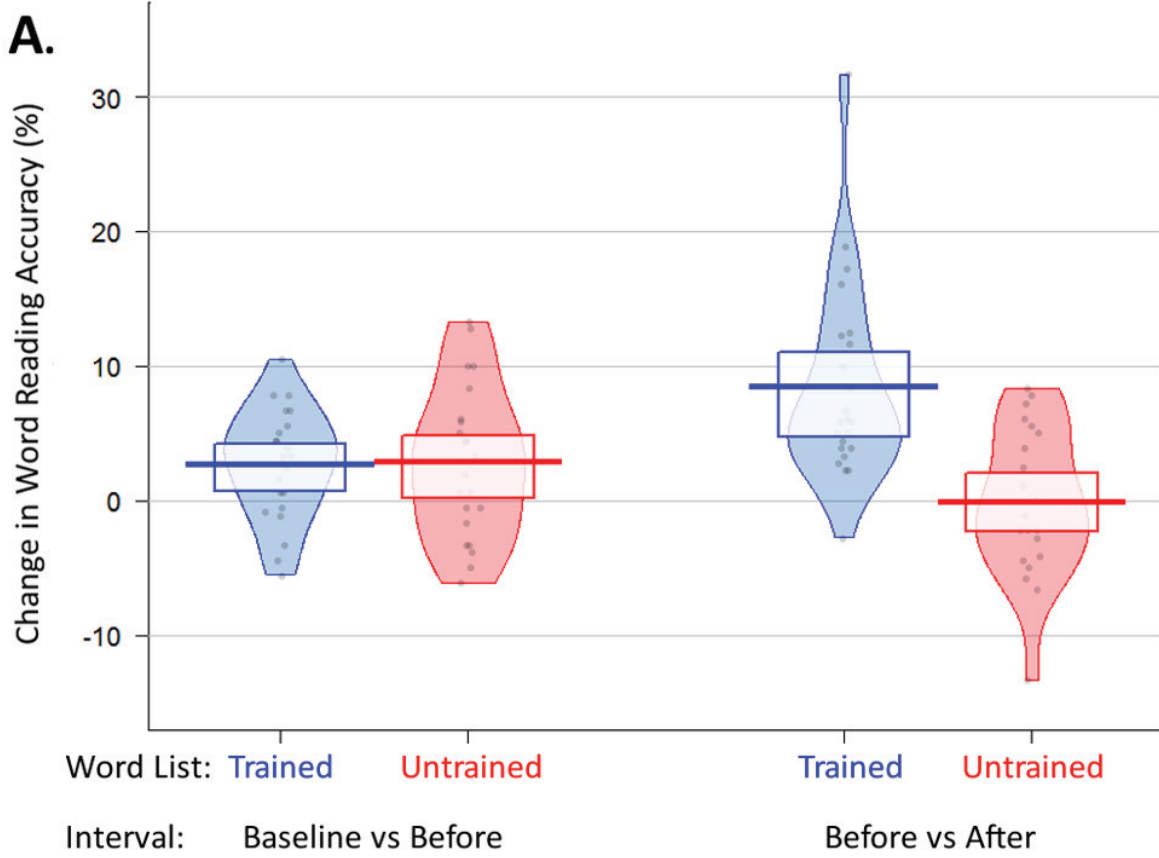
Right Hemisphere



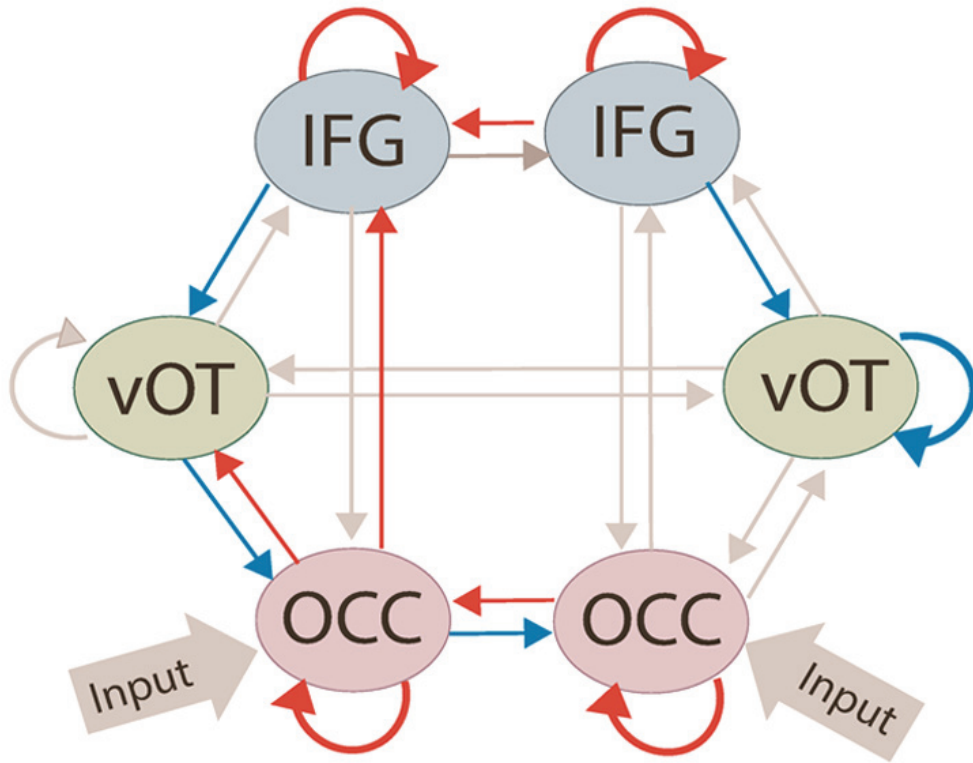
B.







Group-level effects of iReadMore therapy on the reading network



- Weaker after training**
- Stronger after training**

ID	Age (years)	Gender	Time post- stroke (months)	Lesion Volume (cm ³)	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

1