Final Study Report

Study name

Imaging the neural correlates of cholinergic and behaviour driven rehabilitation in patients with Wernicke's aphasia: a double-blinded, cross-over, randomised controlled trial.

Investigator

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Study identifiers

Local Research Ethics number:	05/Q0512/134
UCL Data Protection Ref. No.	Z6364106/2005/8/19
EudraCT No:	2005-004215-30
Sponsors reference (UCL R&D):	BRD/05/155
Sponsors reference (UCLH):	05/N087

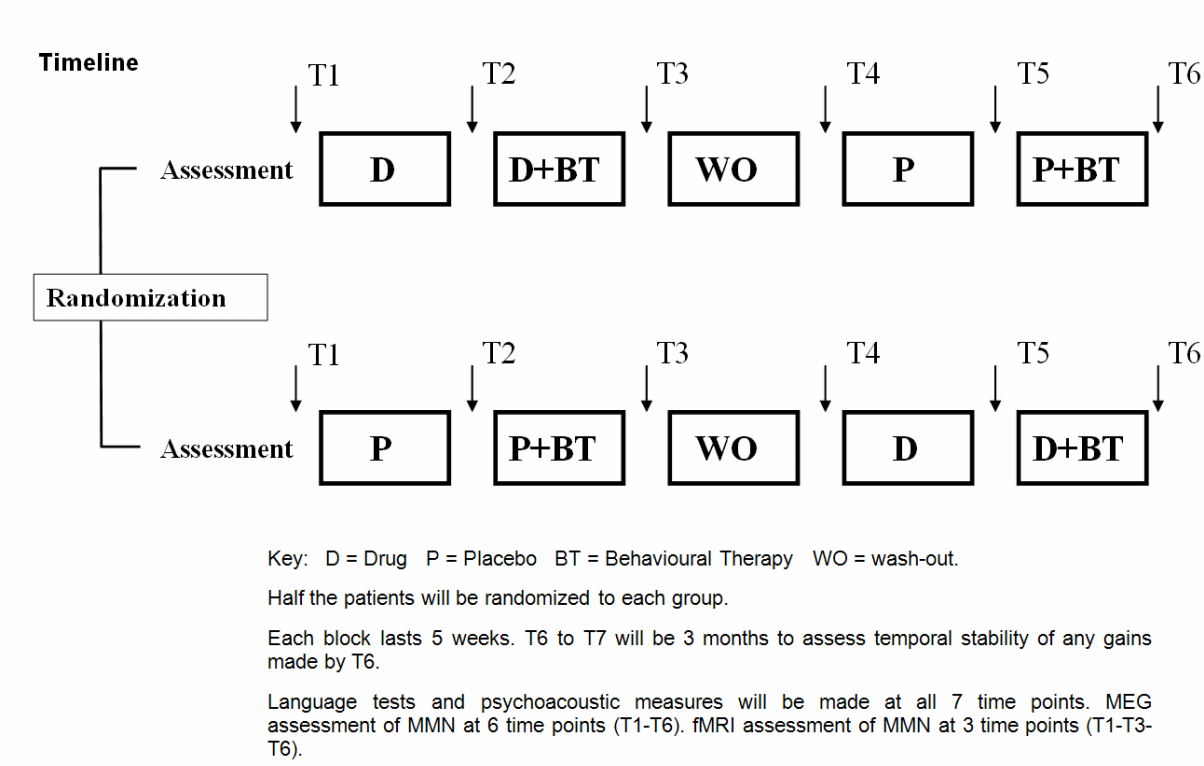
International Standard Randomised Controlled Trial Number (ISRCTN): ISRCTN68939136

Department of Health National Research Register: N0263181161

Study description and design

An interventional, longitudinal study with behavioural and imaging data collected at six timepoints (every 5 weeks, for 6 months). Patients were given two therapeutic agents, an Investigational Medicinal Product (IMP): donepezil, and a behavioural therapy (Earobics). The IMP was placebo controlled in a cross-over trail design so all patients that completed the study received: donepezil, placebo and the Earobics therapy programme. The Earobics therapy was not paired with a behavioural placebo but 50% of the time patients practiced with the Earobics programme, while the other 50% they rested.

Timeline: NB first drug block was 5mg donepezil, second was 10mg donepezil



Recruitment/drop out

27 patients were recruited and 3 dropped out after the first timepoint (baseline). 24 patients completed all 6 timepoints.

Primary outcome measure

This was the correlation between treatment type (donepezil, placebo and Earobics therapy) and change in language function as assessed by performance on the Comprehensive Aphasia Test (CAT).

Behavioural analysis at baseline

The main behavioural outcome measure was a compound score of speech comprehension using the CAT. Interestingly, and unexpectedly, this was binomially distributed at the start of the study (Figure 1: baseline comprehension score). We therefore split the patients into two groups: 'severe' and 'moderate'. We used this subgrouping in the statistical tests below.

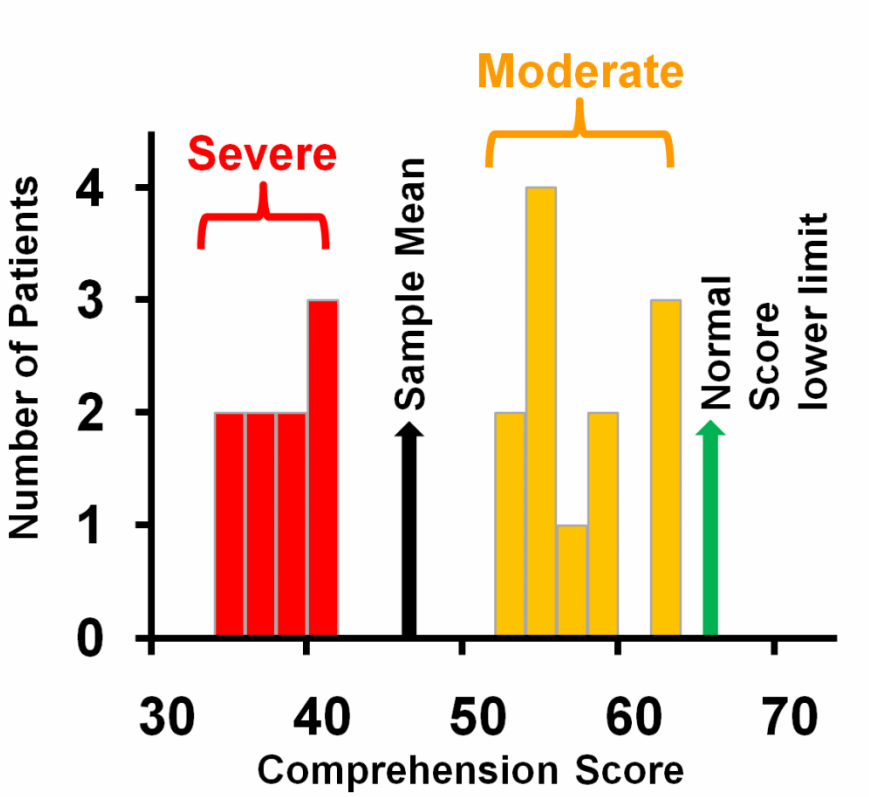


Figure 1

Effect of donepezil versus placebo

Statistical analysis of the main outcome was performed using a 2x2x2 ANOVA. The two within subject factors with two levels each were: drug (donepezil or placebo), and Earobics (therapy block or rest block). The one between subject factor was severity (severe or moderate).

There was a main effect of drug ($p < 0.05$) with an improvement of scores on a compound measure of speech output (speaking) for the patients when on donepezil compared with placebo. There was a trend towards an interaction with group ($p = 0.1$), that is, the more severely affected patients improved more than the moderately affected patients.

Effect of Earobics therapy

There was a main effect of Earobics therapy ($p < 0.05$) with an improvement of scores on a compound measure of speech comprehension (understanding what is being said) for the patients when using Earobics compared with the rest blocks. There was a trend towards an interaction with group ($p = 0.1$), that is, the more severely affected patients improved more than the moderately affected patients.

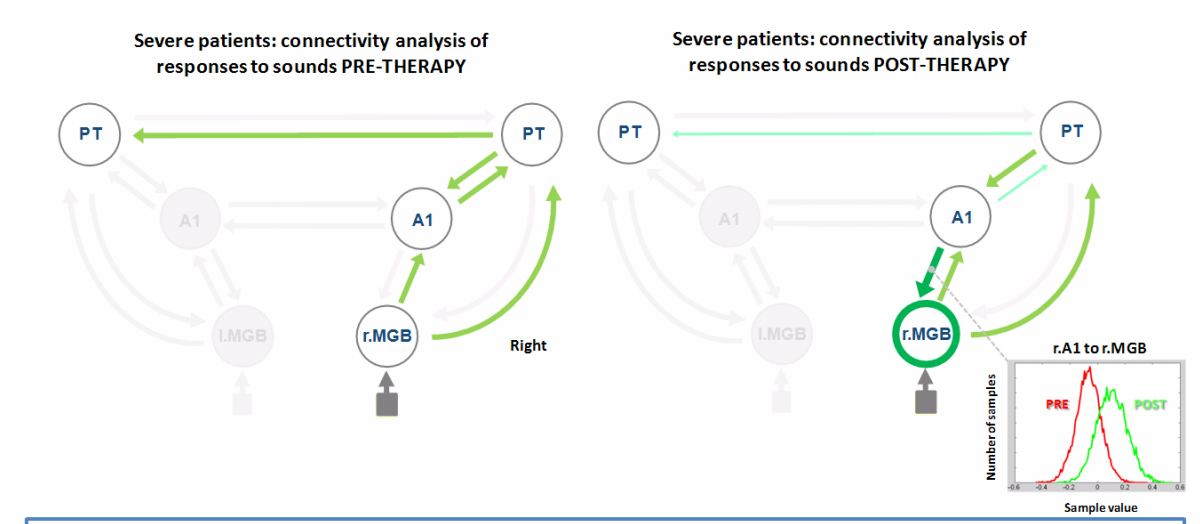
There were no significant interactions between donepezil and Earobics therapy.

Secondary outcome measures

Therapy-induced differences in the task-dependent activity as measured using functional imaging techniques (MEG and fMRI) in the patients groups.

These analyses are ongoing. A preliminary analysis in the severe patient group shows changes in the connectivity of the auditory system induced by the Earobics therapy (Figure 2: PT = planum temporale; A1 = primary auditory cortex; r.MGB = right medial geniculate nucleus).

Figure 2



• Pre-therapy, while listening to speech in the fMRI scanner, the severely impaired patients showed significant modulation of the connections in green (as judged by an analysis of connectivity: Bayesian Model Averaging).
• Post-therapy, two of these connections were significantly strengthened: the backwards connection from A1 to MGB and the self-connection at the level of MGB (dark green). The group average change in the distribution of values for this connection is shown in the inset. Two connections were significantly reduced: the forward connection from A1 to PT, and the lateral connection between right and left PT (lighter green arrows).
• This suggests that the effect of phonological therapy is primarily on the lower levels of the auditory system, leading to smaller prediction errors being passed on (via forward and lateral connections) through to the higher levels of the auditory system.

Safety

Adverse events

There were 2 adverse events reported in the study, both were of mild severity and resolved. One (dizziness) was judged to be an adverse reaction as this occurred when the patient switched to the higher dose of donepezil (from 5mg to 10mg). A 'failure to escalate' decision was made and the patient was restated on the lower dose of donepezil: the symptom improved. The second patient suffered from leg cramps while on the placebo. This adverse event was graded as not related to the IMP.

Drug versus placebo side-effects (from case report form)

In the case report form, 18 symptoms were checked for at each time point (binary scoring system, either present = 1 or absent = 0). A non-parametric test (Cochran Q) was used to assess whether there was an increase in any symptom type with donepezil versus placebo. There was a weak statistical trend for two symptoms being more common while patients were on donepezil: dizziness (p = 0.1) and pruritis (p = 0.07). However, neither of these symptoms were more common on donepezil when compared with baseline symptom reports (first timepoint).

Publications arising from this study

Published in peer-reviewed journals

Penny WD, Flandin G, Daunizeau J, Stephan K, Friston K, Schofield T & Leff AP.
Comparing Model Families
PLOS Computational Biology 2010 Mar 6(3): e1000709

Schofield T, Iverson P, Kiebel SJ, Stephan KE, Kilner JM, Friston KJ, Crinion JT, Price CJ & Leff AP.
Changing meaning causes coupling changes within higher levels of the cortical hierarchy.
Proceedings of the National Academy of Sciences 2009; 106(28): 11765-11770.

Leff AP, Iverson P, Schofield T, Kilner JM, Crinion JT, Friston KJ & Price CJ.
Vowel-specific mismatch negativity responses in the anterior superior temporal gyrus: an fMRI study.
Cortex 2009; 45(4): 517-526.

Leff AP, Schofield T, Stephan KE, Crinion JT, Friston KJ & Price CJ.
The cortical dynamics of intelligible speech.
Journal of Neuroscience 2008; 28(49): 13209-13215.

Submitted

Schofield TM, Penny WD, Stephan KE, Crinion JT, Thompson AJ, Price CJ and Leff AP
Changes in auditory feedback connections determine the severity of speech processing deficits after stroke.

Brodersen KH, Schofield TM, Leff AP, Ong CS, Lomakina EI, Buhmann JM and Stephan KE.
Generative Embedding for Model-Based Classification of fMRI Data