The impact of phonological versus semantic repetition training on generalisation in chronic stroke aphasia reflects differences in dorsal pathway connectivity

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Abstract

It has been suggested that neuroimaging can be used to inform therapeutic intervention. The current study aimed to determine whether an individual would benefit more from training engaging their intact or damaged neural pathway. Two males with chronic stroke aphasia participated, with DM showing milder disruption of connectivity along the dorsal language pathway relative to JS, according to distortion corrected diffusion-weighted MRI. Each patient received two blocks of six repetition training sessions over two weeks, one of which was "phonological" and the other "semantic" in nature. Both phonological and semantic training produced significant gains for both patients for trained items. For the untrained control items, significant gains were specific to training type for each patient. Only phonological training elicited significant generalisation for DM, which was greater than that seen for JS. Conversely, only semantic training elicited significant generalisation for JS, which was greater than that seen for DM. This double dissociation in generalisation effects suggests that a restitutive approach is more effective for patients with milder damage while a compensatory approach may be more effective for those with more severe damage. These results indicate the utility of neuroimaging to optimise relearning strategies and promote generalisation to untrained items.

KEYWORDS: APHASIA, NEUROIMAGING, GENERALISATION, PHONOLOGICAL, SEMANTIC

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There is increasing evidence within speech and language literature of two distinct pathways for language within the human brain (Hickok & Poeppel, 2000, 2004, 2007). Two cortico-cortical pathways project from the bilateral superior temporal gyrus, a region engaged in early speech perception, to form a ventral stream and a dorsal stream. The ventral stream maps between acoustics and articulation via meaning and is implicated in tasks involving auditory comprehension. The dorsal stream maps sound onto articulation which supports sub-lexical speech processing tasks and is crucial for auditory-motor integration of both linguistic and non-linguistic processes. Consistent with this framework, Saur et al. (2008) found that auditory comprehension was subserved by a ventral pathway mediated via the extreme capsule, connecting middle and inferior temporal regions to the ventrolateral prefrontal cortex. In contrast, repetition of nonwords relied upon a dorsal pathway connecting the superior temporal lobe and premotor regions via the arcuate and superior longitudinal fasciculi.

In terms of dysfunction, damage to these two different language pathways has been strongly implicated in aphasia (Binder, Medler, Desai, Conant, & Liebenthal, 2005; Ueno, Saito, Rogers, & Lambon Ralph, 2011). Indeed, different aphasic language profiles support the existence of two simultaneous, parallel anatomical pathways involved in language processing (Friederici & Gierhan, 2013). Disturbance of the dorsal pathway may lead to conduction aphasia, which is characterised by a selective impairment of repetition with preserved comprehension and the production of phonological paraphasias. In contrast, disruption of the ventral route may lead to transcortical sensory aphasia, whose predominant feature is preserved repetition and production in the context of poor comprehension (Kummerer et al., 2013; Noonan, Jefferies, Corbett, & Lambon Ralph, 2010). The degree of lateralisation of function in each processing pathway in the dual-stream model has also been informed by neuropsychological data (Hickok & Poeppel, 2007). The ventral stream is organised bilaterally with each hemisphere supporting different, but complementary parallel

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processing systems. The dorsal stream, on the other hand, is proposed to be strongly left-hemisphere dominant (Berthier, Lambon Ralph, Pujol, & Green, 2012; Catani & Mesulam, 2008)

Although independent, the ventral and dorsal streams are highly interactive. Rolheiser, Stamatakis and Tyler (2011) considered 24 chronic stroke patients' performance across 10 tests involving key aspects of language production and comprehension and how this related to the results of diffusion weighted imaging. Phonological processing was found to load most heavily on the arcuate fascicle, implicated in the dorsal stream (Hickok & Poeppel, 2007). Conversely, semantic tasks were found to load on the extreme capsule, which was implicated in the ventral stream (Hickok & Poeppel, 2007). Importantly, whole-brain correlations showed that only performance on tasks loading strongly on either phonology or semantics fit into this dual-stream model, whereas complex linguistic functions of syntax and morphology required integrity of both pathways (Rolheiser, et al., 2011).

A number of studies have identified that both phonological therapies that engage the dorsal route and semantic therapies that engage the ventral route can produce appreciable improvements in aphasic individuals (e.g., Barthel, Meinzer, Djundja, & Rockstroh, 2008; Bruce & Howard, 1987; Coelho, McHugh, & Boyle, 2000; Fridriksson et al., 2009; Lorenz & Ziegler, 2009; Nettleton & Lesser, 1991; Raymer, Thompson, Jacobs, & Le Grand, 1993). There are however, mixed opinions as to which types of therapy are superior. Some have suggested that semantic treatments may be more effective, based in part on increased generalisation to untreated items immediately post-therapy (Howard, 1985; but c.f. Howard, 2000 for a re-analysis showing equivalent gains). Others have suggested that phonological treatments show stronger immediate gains, but for some patients semantic treatments have greater longevity (Lorenz & Ziegler, 2009).

Nickels (2002) has proposed that a combination of phonology and semantics may be the most effective treatment, consistent with the synergistic view of speech processing via the dorsal and ventral pathways. However, (Howard, 2000) argued that the difference between semantic and phonological tasks is often overstated. For example, in studies that aim to employ a "semantic"

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treatment such as word-to-picture matching, or a yes/no decision task (e.g., is a cat an animal?) the spoken or written phonological form of the target is also provided. Likewise, in "phonological" treatment tasks such as phonologically-cued picture naming semantic activation is also elicited via the presence of a pictorial stimulus. Therefore, both intervention types are engaging the language system in a similar way: by strengthening mappings between semantics and phonology.

There is evidence that the treatment efficacy interacts with nature of the patients' impairment. In a recent study by Best and colleagues (2013), two patient groups were administered an identical phonological cueing treatment for picture naming. One group of patients was classified as having relatively less of a semantic difficulty (as measured by spoken and written word to picture matching) and more of a phonological output deficit (as measured by length effects and phonological errors in picture naming) when compared to the other group. It was the patients with the greater degree of phonological impairment and lesser degree of semantic impairment who then demonstrated generalisation to untreated items. Importantly, outcome did not relate to traditional aphasia classification, but rather was driven by characterisation of retained behavioural skill.

Critically, in previous research considering the relative efficacy of phonological vs semantic therapies, one factor that is rarely considered in determining the patients' response is the nature of that person's underlying brain damage (Abel, Weiller, Huber, Willmes, & Specht, 2015). Neuroimaging is being harnessed to predict recovery (Price, Seghier, & Leff, 2010; Seghier et al., 2016), and could also be utilised to inform intervention. The dual stream model clearly suggests that brain damage can differentially affect the dorsal and ventral pathways, and this has been validated in recent lesion-symptom mapping studies (Butler, Lambon Ralph, & Woollams, 2014). This is obviously a factor that will have some impact on the relative effectiveness of phonological versus semantic treatment strategies. Yet if brain damage does affect one pathway more than the other, then the question becomes whether therapy should focus on rebuilding the function associated with that pathway (e.g., a phonological therapy for a patient with dorsal damage) or rather enhance the

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use of relatively intact pathways (e.g., a semantic therapy for a patient with dorsal damage). The general issue as to whether therapy should be impairment-focused (e.g., Coelho, et al., 2000; Fridriksson, et al., 2009; Louis et al., 2001; Nettleton & Lesser, 1991) or draw upon intact processing abilities (Yampolsky & Wayers, 2002) is a matter of ongoing debate in the literature.

The goal of this study is to explore how the underlying neuropathology interacts with intervention type in terms of both direct therapeutic gains and the potential for generalisation to untrained items. Using the dual-stream model as a basis to inform therapy for word repetition difficulties, the current study aimed to determine whether an individual would benefit more from restitutive training to restore the function of the damaged neural pathway or compensatory training that takes advantage of the function of the intact neural pathway. Word repetition was selected as the target as this is a "degenerate" task (Price & Friston, 2002) that can be accomplished via either the dorsal or ventral pathways. Furthermore, the ability to repeat is often a capacity required in order to effectively engage with most traditional therapeutic interventions for word finding difficulties (e.g., Abel, Schultz, Radermacher, Willmes, & Huber, 2005; Bastiaanse, Bosje, & Franssen, 1996; Nickels, 1992, 2002). We employed a phonological and a semantically oriented relearning protocol to tap the capacity of the damaged dorsal and intact ventral pathways respectively. We compared the effectiveness of phonological vs. semantic therapy for repetition in two individuals, patients DM and JS, with differential degrees of damage to the dorsal language pathways, as determined by Diffusion Tensor Imaging and subsequent probabilistic tractography (Anatomical Connectivity Mapping).

2. Material and Methods

2.1. Patients

Two native English speaking, right-handed males (DM and JS) with chronic stroke aphasia were recruited from a larger study concerning the role of white matter connectivity in chronic stroke aphasia (Butler, et al., 2014). Both patients had a single left-hemisphere stroke, more than one year previous, resulting in chronic stroke aphasia. Both DM and JS are classified as Broca-type aphasic speakers and were impaired on the Cambridge 64-item picture naming test (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000; Hodges, Patterson, Oxbury, & Funnell, 1992) and the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983). Table 1 provides demographic information and summarises the performance of the patients on a variety of neuropsychological tests. For those neuropsychological tasks without published normative data, Butler et al. (2014), collected control data from healthy control participants (three females, 10 males): mean age = 68.69 years (SD = 6.55), range = 59–80 years; mean years of education = 12.55(SD = 2.38), range = 10–17 years.

In comparison to control data, both patients showed impairments across assessments that engaged phonological and semantic knowledge. For example, both patients were impaired at repetition, suggesting that the dorsal pathway is most likely damaged. However, repetition of known words may also be achieved via meaning and thus the ventral pathway. DM is impaired at all repetition tasks, JS only at immediate repetition of words and nonwords. Patient JS was impaired at the synonym task and the Camel and Cactus picture association task, which could be ascribed to damage to the ventral pathway, but the synonym task also involves a speech perception component that is mediated by the dorsal pathway. Both patients were impaired on the spoken sentence comprehension task: a task that relies upon both the dorsal pathways for processing of the spoken input and ventral pathway for access to meaning. Given these intricacies of standardised assessments across phonological and semantic boundaries the degree of damage to the dorsal and ventral pathways cannot be easily identified on the basis of behavioural profile alone.

Neither of the patients was receiving any individual or group therapy for the treatment of naming deficits during the course of this study, but both have a history of speech and language treatment. Both patients and their carers gave informed consent to participate in the study in accordance with the NHS approved ethics associated with the study.

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	DM	JS
Demographic data		
Age (Years)	49	78
Gender	M	M
Years of Education	17	12
Time post-stroke (months)	42	76
BDAE Classification	Broca	Broca
Repetition		
Word: Immediate	**73.75**	**90**
Word: Delayed	**68.75**	91.25
Nonword: Immediate	**60**	**36.67**
Nonword: Delayed	**10**	63.33
Naming		
64-Item Naming	**75**	**71.88**
Boston Naming Test	**71.67**	**53.33**
Auditory Judgement		
Minimal pairs: Words	93.06	86.11
Minimal pairs: Nonwords	80.56	**75**
Comprehension		
Spoken word-to-picture match	98.44	98.44
Written word-to-picture match	98.44	98.44
Camel and Cactus Test	98.44	**76.04**
CAT Spoken sentence comprehension	**56.25**	**75**
Synonym judgement	95.83	**76.04**
Cognitive		
Brixton Spatial Anticipation Test[a]	50.91	43.64
Raven's Coloured Progressive Matrices[b]	91.67	77.78
Forward Digit Span[a]	**37.5**	62.5
Backward Digit Span[a]	**0**	42.86

Table 1: Demographic and behavioural assessment battery scores for each participant as measured at the time of their brain scans. Scores are given as percentages. Scores marked in bold fall below the cut-off for normal performance. The cut-off was calculated as 2 SD below the mean control performance. [a] Cut-off based on published norms. [b] No cut-off available.

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2.2. *Stimuli*

Experimental stimuli for the pre-test consisted of a set of 240 words varied by imageability (120 low; 120 high imageability words). Both high and low imageability sets were matched for overall frequency according to the Kucera and Francis (Kucera & Francis, 1967) and CELEX (Baayen, Piepenbrock, & Gulikers, 1995) measures, number of syllables and phonemes (MRC psycholinguistic database, Coltheart, 1981). Training stimuli were individualised for each patient and drawn from words that patients failed to accurately repeat on both of the pre-testing occasions. For each patient, consistently failed items were then split into four matched sets of fifteen words that comprised the relearning conditions (phonological or semantic) with the remaining two sets as untrained control for each relearning condition. For each patient, t-tests revealed no significant differences on any of the psycholinguistic measures across training and control sets used in each therapy, nor across training and control sets within each condition (all t-values < 1 for both patients, p-value ranges from 0.35 – 1). Although the two patients received different items, the training and control stimuli were matched as closely as possible across patients in terms of imageability, frequency and word length (number of syllables, phonemes and letters). Nevertheless, stimuli for DM tended to be somewhat longer than for JS. In particular syllable length of the phonological training ($t=2.30$, $df = 28$, $p=0.03$) and control set ($t=2.59$, $df = 28$, $p=0.02$) were greater for DM than JS. Likewise, the semantic training and control condition were also longer in terms of the number of syllables for DM (training: $t=2.14$, $df = 28$, $p=0.04$; control: $t=2.96$, $df = 28$, $p=0.006$) than JS. Despite these differences in length measures, imageability and frequency measures were closely matched across patients (all t values <1.35). See Table 2 for average measure values for each participant in each condition.

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	Length		Frequency		Imageability
	Syllables	Phonemes	K&F	CELEX	
DM					
Phonological	2.67	6.73	46.87	581.47	467.47
Phonological Control	2.73	7.33	47.67	607.20	458.20
Semantic	2.67	7.07	44.07	681.47	449.00
Semantic Control	2.73	6.53	46.33	629.60	453.53
JS					
Phonological	2.07	5.00	37.87	724.80	458.20
Phonological Control	2.07	4.93	36.13	835.27	499.60
Semantic	2.13	5.60	36.73	780.00	482.93
Semantic Control	2.00	5.20	36.93	622.27	479.53

Table 2: Mean stimulus properties for each condition for each patient.

2.3. Procedure

Two pre-training assessments separated by one week were conducted to establish baseline repetition performance of the 240-item experimental stimuli. At each pre-training assessment time points, patients were required to immediately repeat each heard word as quickly and as accurately as they could. A fixation cross appeared on a computer screen to signal the end of the auditory stimuli and prompt a response. Repetition was self-paced and a keypress was required to initiate the next trial. Training sessions then began a week after the second pre-training assessment session. Verbal responses in the pre-training assessments, baseline assessments, training sessions, and post-training assessments were digitally recorded for offline coding of response accuracy.

2.4. Training protocol

Training blocks consisted of three one-hour sessions per week for two weeks with each patient receiving a total of twelve sessions over two training blocks. Training was either “phonological” or “semantic” in nature with both training conditions requiring that patients repeat each heard word. In the phonological condition,

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each heard word was accompanied by a video of a mouth saying the same word simultaneously. Such audio-visual integration has been shown to not only improve picture naming performance in aphasic speakers on both trained and untrained items but also created an "errorless learning" environment which patients found particularly enjoyable (Fridriksson, et al., 2009). Fridriksson and colleagues (2009) demonstrated that treatment of speech production in non-fluent aphasic patients can make use of motor speech perception, even though this process is also somewhat impaired in aphasia (Schmid & Ziegler, 2006). Perception of audio-visual speech activates left frontal regions also involved in speech production; hence the use of such stimuli aphasia therapy aims to activate these regions to stimulate any residual function. In contrast, in the semantic training condition, each heard word was paired with an associated picture (e.g., high imageability: "beef" with a picture of a sliced roast; "bandage" with a picture of an arm being bandaged; low imageability: "hazard" with a picture of a warning sign, "envy" with a picture of a green eye). We used pictures of a concrete associates in order to allow the same therapy approach for both high and low imageability items (Hoffman & Lambon Ralph, 2011) although of course the word referent was more often present in the picture for the high imageability words than the low imageability words. Stimuli were presented using the DMDX software (Forster & Forster, 2003) on a Dell Laptop. Presentation was self-paced with each therapy session consisting of six repetitions of the 15 item training set, with each block of the set randomised anew.

Each patient received two blocks of training, with one block consisting of six semantic sessions and the other block consisting of six phonological sessions, the order of which was counterbalanced across patients (DM received semantic training first, while JS received phonological training first). Training sessions were equally spaced within each week of the training block. Before beginning the first training block, each patient was retested on the training and control items for that training block condition to provide a current baseline measure. After completion of the first training block, patients' repetition performance was immediately assessed on their trained and matched control words. Maintenance of any gains was determined by a follow-up assessment one week later. Before beginning the second training block, each patient was retested on the training and control items for that training block condition to provide a revised baseline measure. Immediate gains in word repetition at the second training block and at one-week follow-up were again assessed (see Figure 1 below for protocol).

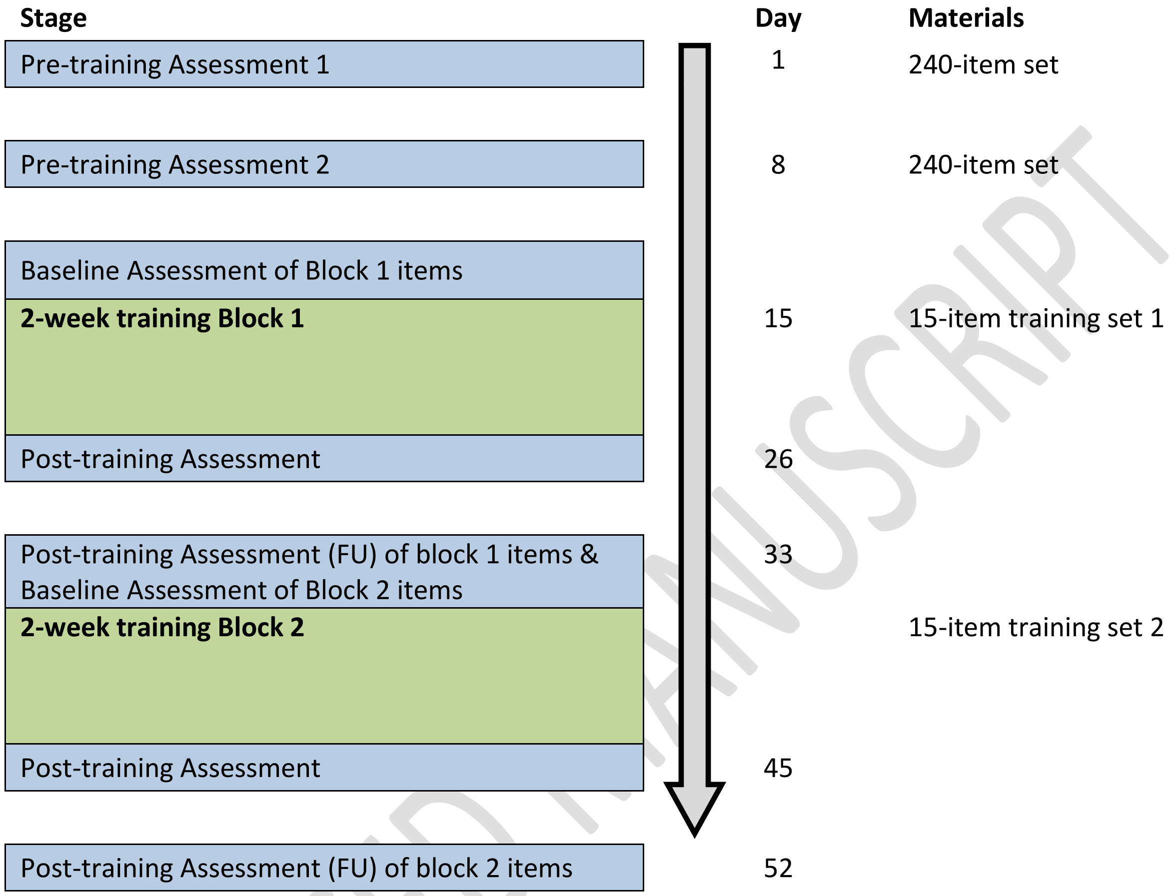

Figure 1: Schematic of study design. Assessment days are highlighted in blue. Training blocks are highlighted in green. If set 1 corresponded to the phonological training items, set 2 would therefore correspond to the semantic items and vice versa.

2.5. Acquisition of Imaging Data

Patients' imaging data were acquired as part of a larger case series study by Butler, Lambon Ralph, and Woollams (2014). All scans were acquired on a 3T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) using an 8-element SENSE head coil. High resolution structural MRI scans were acquired using a T1-weighted inversion recovery sequence with 3D acquisition, with the following parameters: TR (repetition time) = 9.0 ms, TE (echo time) = 3.93 ms, flip angle = 8 °, 150 contiguous slices, slice thickness =

1 mm, acquired voxel size 1.0 mm x 1.0 mm x 1.0 mm, matrix size 256 x 256, FOV = 256 mm x 256 mm, TI (inversion time) = 1150 ms, SENSE acceleration factor 2.5. Distortion corrected diffusion-weighted images were acquired using a pulsed gradient spin echo echo-planar imaging sequence implemented with TE = 54 ms, G_{max} = 62 mT/m, half scan factor = 0.679, 112 x 112 image matrix reconstructed to 128 x 128 using zero filling, reconstructed resolution 1.875 mm x 1.875 mm, slice thickness 2.1 mm, 60 contiguous slices, 43 non-collinear diffusion sensitization directions at b = 1200 s/mm^2 (Δ = 29.8 ms, δ = 13.1 ms), 1 at b = 0, SENSE acceleration factor = 2.5. Artefacts arising from pulsatile brain movements (Jones & Pierpaoli, 2005) were minimised by cardiac gating the diffusion sequence using a peripheral pulse unit placed on the participant's finger. Acquisition time for the diffusion MRI data was approximately 28 minutes, although this varied slightly based on the participant's heart rate. For each diffusion gradient direction, phase encoding was performed in right-left and left-right directions, giving two sets of images with the same diffusion gradient directions but opposite polarity *k*-space traversal, and hence reversed phase and frequency encode direction, allowing correction for geometric distortion (Embleton, Haroon, Morris, Ralph, & Parker, 2010). A co-localised T_2 weighted turbo spin echo scan with 0.94 mm x 0.94 mm in-plane resolution and 2.1 mm slice thickness was also obtained for use as a structural reference scan in distortion correction (Embleton, et al., 2010).

2.6. Pre-processing of Imaging Data

Pre-processing of T1-weighted data was conducted in SPM8 (SPM8, Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/). Patients' T1-weighted scans were normalised and segmented, together with 19 age- and education-matched healthy control patients' brains using a modified unified normalisation-segmentation procedure (Seghier, Ramlackhansingh, Crinion, Leff, & Price, 2008). The normalised images were then smoothed using an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel. Susceptibility- and eddy current-induced distortions in diffusion data were corrected using Embleton's et al.'s (2010) distortion correction method implemented in MATLAB. Distortion-corrected diffusion weighted images were then processed using the model-based bootstrap (Haroon, Morris, Embleton, & Parker, 2009), applied to constrained spherical deconvolution (CSD) (Tournier, Calamante, &

Connelly, 2007; Tournier et al., 2008). The bootstrapped CSD was used to derive probability density functions (PDFs) that were used to produce whole brain probabilistic tractography-derived connection maps called Anatomical Connectivity Maps (ACMs) (Embleton, Morris, Haroon, Lambon Ralph, & Parker, 2007). ACMs quantify the total number of probabilistic paths recorded passing through each voxel of the brain, thereby providing a measure of the degree of tractography-derived anatomical connectivity passing to, from and through each voxel. ACMs were generated using the probabilistic index of connectivity (PICo) tractography algorithm (Parker, Haroon, & Wheeler-Kingshott, 2003), with ten tractography streamlines launched from every brain voxel. Each participant's T1-weighted image and ACM were co-registered using a rigid-body transformation and normalised to Montreal Neurological Institute (MNI) space in SPM8. All coordinates are reported in MNI space.

3. Results

3.1. Behavioural data

Raw repetition accuracy scores for each patient at each time point for each intervention type (semantic or phonological) relative to a matched control condition are reported in Table 3. The number of items incorrect at baseline that were then correct after training is provided in parentheses.

Gains relative to baseline: Considering data for those items that were incorrect at baseline, Exact McNemar tests (one-tailed) revealed that patient DM showed a significant increase in word repetition accuracy for trained items immediately after the phonological (χ^2 =5.14, p=.008) and semantic training conditions (χ^2 =5.14, p=.008), both of which were maintained at follow up (χ^2 =5.14, p=.008; χ^2 =5.14, p=.008). The control conditions also showed a significant increase immediately after phonological training (χ^2 =3.20, p=.031), which was marginal at follow up (χ^2 =2.25, p=.062), and contrasted with the lack of significant changes to the control items after semantic training (χ^2 =0.50, p=.250, χ^2 =0.50, p=.250).

Patient JS also showed significant improvement in word repetition accuracy for trained items after both the phonological (χ^2 =8.10, p=.001) and semantic (χ^2 =7.11, p=.002) training conditions, which were again

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maintained at follow up (χ^2 =4.17, p=.016, χ^2 =5.14, p=.008). JS showed no reliable gains for control items in the phonological training condition with performance remaining at zero correct at both post-training assessment time points, but did show a significant improvement on control items for the semantic training condition (χ^2 =4.17, p=.016), although not maintained at follow-up (χ^2 =1.33, p=.125).

In summary, both phonological and semantic therapy was produced significant gains for both patients for trained items. What is more interesting are the results for the untrained control items, which showed significant increases for the phonological condition only for DM and the semantic condition only for JS. While it could be argued that increases for control items were a simply the result of contact associated with the process of training, the fact that these gains were not general but specific to training type, and indeed to different training types across patients, suggests that these effects may instead be better viewed as effective generalisation.

Training Condition		**Patient DM**			**Patient JS**		
		Pre	**Post**	**FU**	**Pre**	**Post**	**FU**
Phonological	Trained	1	8(7)	8(7)	0	10(10)	6(6)
	Control	1	5(5)	5(4)	0	0(0)	0(0)
Semantic	Trained	0	7(7)	7(7)	2	11 (9)	8(7)
	Control	0	2(2)	2(2)	1	6(6)	4(3)

Table 3: Number of items correct for each training condition for each patient, with the number of items incorrect at baseline but correct after training in parentheses. Pre = baseline performance before training block; Post = immediately post training; FU= one week follow-up.

Comparison of gains over treatments: Calculation of the magnitude of gains (i.e., the proportion of trained and control items incorrect at baseline that were correct after training) are shown in Figure 2.

For DM, semantic and phonological training was equally effective for trained items both immediately and at follow up (χ^2 =0.03, p=.857; χ^2 =0.03, p=.857). For control items, phonological training was more effective than the semantic training immediately (χ^2 =1.58, p=.159) and at follow-up (χ^2 =1.03, p=.311), although this difference did not reach significance. This difference in performance for control items over training type meant that the advantage of trained over untrained items was significant for the semantic condition (immediate: χ^2 = 3.97, p=.046; follow-up: χ^2 = 3.97, p=.046) but not the phonological condition (immediate: χ^2 =0.58, p=0.446; follow-up; χ^2 = 1.35, p=.244). It is important to note that while this latter contrast could be taken as indicating greater treatment gains for the semantic condition for DM, if we take control item performance as indicating generalisation, the opposite is true (net gains over trained and untrained of 12/11 items for phonological vs 9/9 items for semantic immediately and at follow-up, respectively).

For JS, semantic and phonological therapy were also equally effective for trained items both immediately (χ^2 =0.02, p=.885) and at follow up (χ^2 =0.53, p=.464). For control items, semantic training was significantly more effective than the phonological training immediately (χ^2 =8.11, p=.004) and marginally so at follow-up (χ^2 =3.59, p=.058). The advantage of trained over untrained items was clearly significant for the phonological condition (immediate: χ^2 =15.00, p<.001, follow-up: χ^2 =7.50, p=.006) but was only marginally so at follow-up for the semantic condition (immediate: χ^2 =1.90, p=.168; follow-up: χ^2 =3.04, p=.082). Again, this could be taken as indicating greater treatment gains for the phonological condition for JS, but if we take control item performance as indicating generalisation, the opposite is clearly the case (net gains over trained and untrained of 10/6 items for phonological vs 15/10 items for semantic immediately and at follow-up, respectively).

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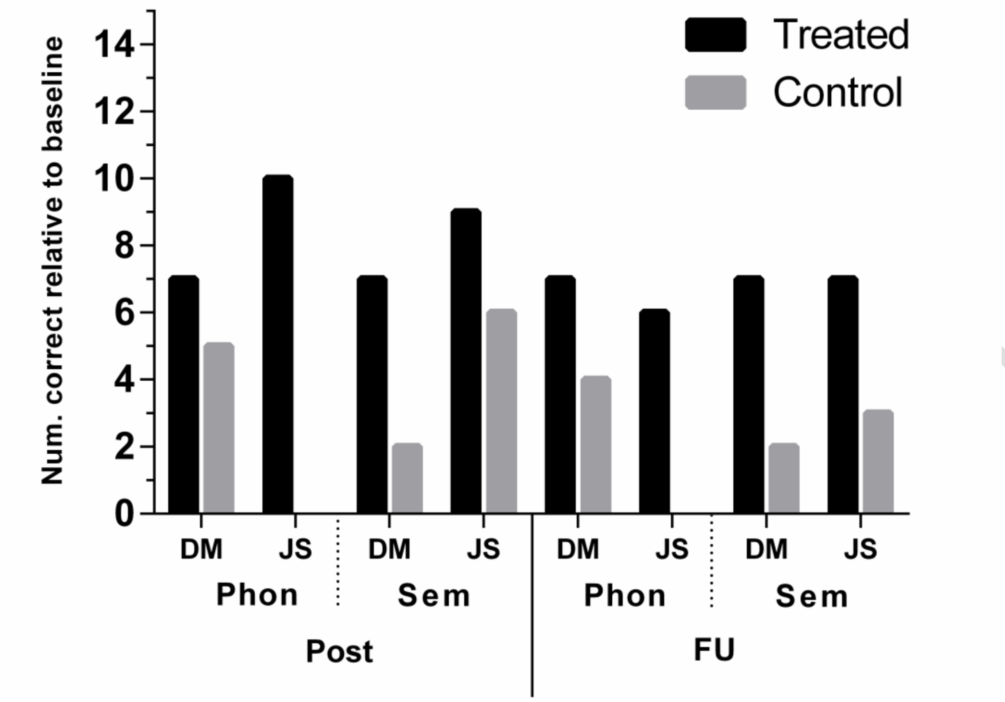

Figure 2: Number of items incorrect at baseline but correct after training for patients DM and JS. Post = immediately post training; FU= one week follow-up.

Comparison of gains over patients: For the trained items, there were no significant differences in the overall extent of gain made by patients after either the phonological (χ^2 = 0.8266, p=.3620) or the semantic (χ^2 = 1.45, p=.229) condition immediately post training, or at follow up (phonological: χ^2 = 0.29, p = 0.584; semantic: χ^2 = 0.14, p = 0.705). However, direct comparison of the overall gains made by each patient after each training condition for *control* items showed a striking interaction: patient DM repeated significantly more control items following phonological therapy than patient JS both immediately and at follow-up (χ^2 = 6.47, p=.011; χ^2 = 4.97, p=.025;). Conversely, patient JS repeated marginally significantly more control items following semantic therapy than patient DM (χ^2 = 3.16, p=.075), although this difference was not maintained at follow-up due to a decay of JS's gains (χ^2 = 0.333, p=.564).

The behavioural results therefore suggest an initial double dissociation over patients in the effectiveness of training on performance for untrained items. Given the internal control provided by the within-subject cross-over design and pairwise matching of training and control sets on a variety of psycholinguistic variables, a key factor that may support differing generalisation effects observed in each patient result from variation in the nature of the patient's brain damage. We consider not only the integrity of grey and white matter, but also the degree of reductions in connectivity along white matter pathways in each patient using ACMs. According to the dual stream model of speech processing, we would expect that differences between patients in damage to the dorsal and/or ventral pathways may have mediated the differential generalisation of training effects to control items.

3.2. Neuroimaging data

T1 weighted structural images revealed that patient DM had damage to the left temporo-insula region (top panel, Figure 3). Damage extended anteriorly to the posterior aspect of the frontal lobe, specifically the ventral premotor cortex. The primary locus of damage was the supra-temporal plane, including Heschl's gyrus. The inferior extending to the superior aspect of the parietal lobe, including the angular and supramarginal gyrus were also damaged. In addition, the insula has been mostly damaged extending medially to left subcortical regions of the caudate and putamen.

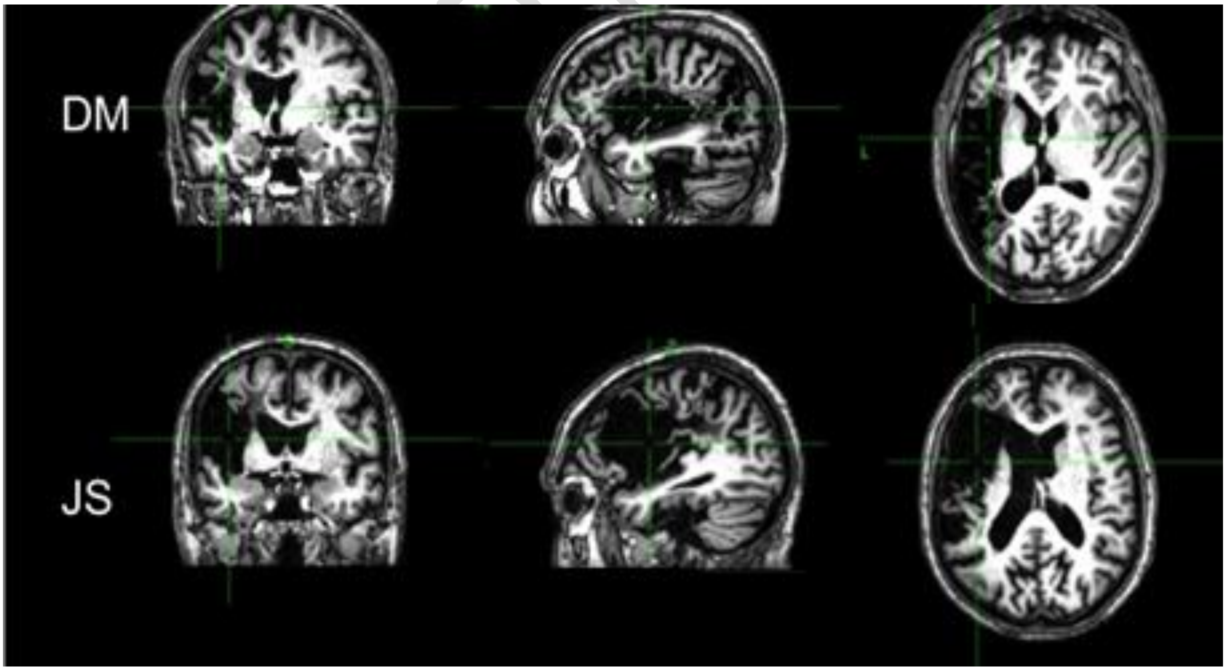

Figure 3: T1 images for each patient showing their left hemisphere lesions. Coronal slices (left), sagittal slices (centre) and axial slices (right).

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JS also had left hemisphere damage restricted to the left frontal and anterior insula region (lower panel, Figure 3). Frontal damage extended anteriorly to the middle frontal gyrus affecting the pars orbitalis and triangularis gryi of Broca's area and posteriorly to the precentral gyrus. In addition, the insula has been mostly damaged with further damage to left subcortical regions including the head of the caudate. The posterior supra-temporal plane, including Heschl's gyrus were unaffected with the planum temporale largely spared. Measurement of total normalised lesion volume revealed that the extent of DM's lesion was 11919 voxels; patient JS's normalised lesion volume was greater at 18445 voxels. However, despite a greater lesion volume, JS's relative gains in training – identified in the behavioural analyses above – immediately post therapy for trained items were not significantly different from DM or dependent upon therapy type. Thus the significant interaction between patient and therapy type on generalisation of gains to control items does not seem entirely attributable to differences in the size of the lesion.

Each patient's ACM image of white matter integrity show reduced anatomical connectivity in the left hemisphere (Figure 4, panels A and B) compared to right sagittal view. To determine the location and extent of damage to key tracts that mediate dorsal and ventral pathway function, we compared the patients' connectivity to standard templates (Figure 4, panel C). Each patient's ACM in standard space was used as a mask against the SPM white matter template image. Resulting images were then overlaid with standardised white matter tract images (Anatomy toolbox plugin for SPM, Eickhoff et al., 2005) of the dorsal and ventral pathways (Figure 4, panels D and E). The overlays highlight the loci and extent of damage to the arcuate fascicle, including the anterior, longitudinal and posterior segment of the dorsal pathway.

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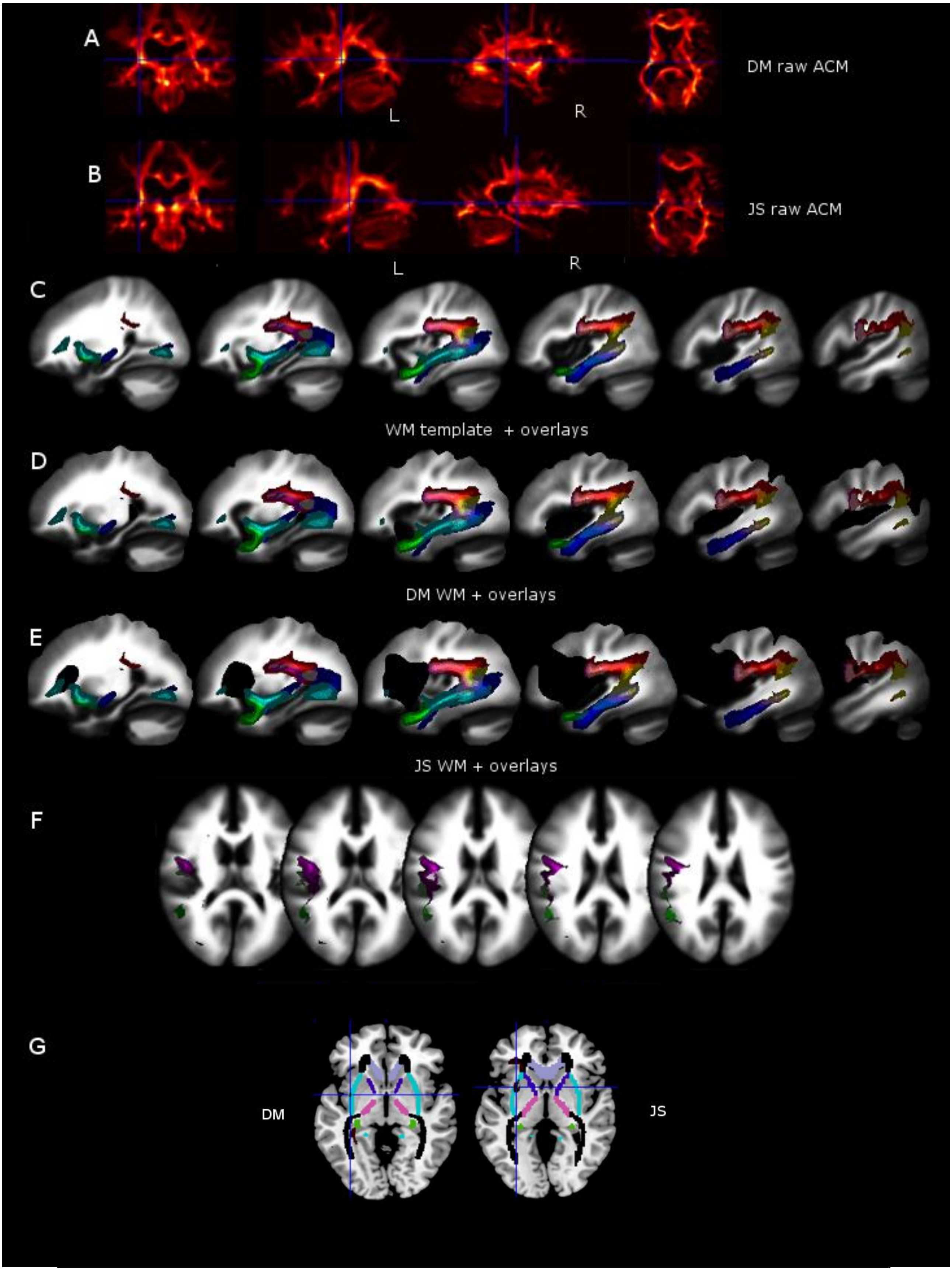

Figure 4: Panel A and B show the raw ACMs for each patient which reveal reduced anatomical connectivity within the left hemisphere for both patients. Panel C shows the standard white matter template from SPM overlaid with standardised white matter tract images of the ventral and dorsal pathways. The dorsal tract is comprised of the arcuate fascicle (red), including the anterior (pink), longitudinal (violet) and posterior

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segments (yellow). The ventral tract is comprised of the inferior longitudinal (blue), inferior-occipital (cyan) and uncinate fasciculus (green) portions. Panels D and E show the standard SPM white matter template masked by each patient's smoothed and warped ACMs. Resulting images show regions of white matter integrity loss overlaid with standardised white matter tract images to show location and extent of damage for each patient. Panel F shows difference in location and extent of white matter damage for patients DM (green) and JS (violet) relative to standardized white matter segments of the dorsal and ventral pathways. Panel G shows for both patients with relatively minimal ventral damage identified in the external capsule (cyan).

In order to isolate and quantify the damage to connectivity along the dorsal and ventral pathways for each patient, smoothed and normalised ACMs were used as a mask against the standard SPM template. The resulting image was then subtracted from the template to generate a difference image for each patient. These difference images were then overlaid on the white matter template to highlight the differing extent of damage to underlying white matter connectivity. Both patients had disruption to the integrity of the arcuate fasciculus, the key tract of the dorsal pathway. This is consistent with the known role of the arcuate fasciculus in repetition (Saur, et al., 2008) and the nonword repetition deficits seen in both DM and JS. DM had moderate damage along the arcuate fascicle, focussed in the posterior segment (highlighted in green in panel F of Figure 4) of the dorsal pathway, while JS had more severe damage along the arcuate fascicle, particularly at the intersection of the anterior and longitudinal segment (highlighted in violet in panel F of Figure 4).

Inspection of the integrity of the ventral pathway (Figure 4, panels D and E) showed no evidence of damage to the uncinate, inferior longitudinal or inferior occipital segments. However, these templates do not consider the external capsule, a component of the ventral pathway (Bajada, Lambon Ralph, & Cloutman, 2015; Parker, et al., 2003). Additional inspection of the ACMs against the JHU template as implemented in MRIcroN (Rorden, Karnath, & Bonilha, 2007) showed very minor damage to the external capsule for DM. For JS, more pronounced damage to the external capsule was apparent, (panel G of Figure 4). In both cases, the damage to the ventral pathway was much less than that for the dorsal pathway. Moreover, the degree of external capsule damage would lead us to expect greater potential benefits from semantic therapy for DM than JS, where in fact the opposite pattern was observed.

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4. Discussion

Our comparison across two patients with Broca's aphasia showed that for each patient there were significant and equivalent gains in naming accuracy on trained items after both phonological and semantic relearning strategies that were maintained at one week follow up. Both patients also showed generalisation to untrained, control items. What was striking was that patients' generalisation of gains to control items was specific to particular training conditions. Only phonological training elicited generalisation to control items for DM and only semantic training elicited a significant generalisation for patient JS. Interpretation of these generalisation effects in the context of a neuropsychological profile alone is challenging as the dorsal and ventral processing pathways cooperate to support language processing. Neuroimaging data concerning connectivity along the dorsal and ventral pathways indicated that the differential benefits of phonological and semantic relearning strategies to naming accuracy of control items corresponded to the variation in the extent and loci of damage to the arcuate fasciculus.

The results DM and JS for trained items provide further support that semantic and phonological therapies can produce appreciable improvements in individuals with aphasia (Howard 2000; Best & Nickels, 2004). The training regimes used here were based upon theoretically motivated treatments that have been successfully used in therapy studies (c.f. Hickin, Best, Herbert, Howard, & Osborne, 2002). Furthermore, the results support the view that semantic and phonological therapies are both viable treatments for anomia in aphasic individuals (Barthel, et al., 2008; Bruce & Howard, 1987; Coelho, et al., 2000; Fridriksson, et al., 2009; Lorenz & Ziegler, 2009; Nettleton & Lesser, 1991; Raymer, et al., 1993). The gains observed for trained items following the phonological training strategy in DM and JS also provide support for using visual speech perception as a viable way to improve speech production (Fridriksson, et al., 2009). Moreover, the gains observed for both DM and JS following the semantic relearning strategy suggests that using a computer-based paradigm in which words are paired with associated objects can also produce improvements in patients with Broca's aphasia. This is particularly useful as it allows semantically based training on words with less imageable meanings that may be of more use in everyday communication. In summary, our results clearly indicate equivalent and significant benefits from the phonological and semantic training regimes for the trained items.

In contrast, phonological and semantic relearning strategies elicited generalisation to untrained control items that was specific to a particular training condition. Despite both patients engaging with each type of training, the differential pattern of generalisation was clear. DM showed generalisation to only after phonological training, and this was significantly greater than that seen for JS both immediately and one week later. In contrast, JS showed generalisation only after semantic training, and this was marginally significantly greater than that seen for DM immediately. The results for JS agree with Howard's (1985) suggestion that semantic training leads to more generalisation to untrained items, but this immediate generalisation decayed to non-significance at one week follow up. This view is incongruent with the greater generalisation from phonological training seen for DM, which demonstrates that generalisation effects are not solely determined by therapeutic approach. It would have been difficult to anticipate this differential generalisation from a comparison of the patients' neuropsychological profile.

Analyses of the impact of the patients' lesions on the connectivity on their dorsal and ventral processing pathways, however, did show some correspondence with the differential generalisation observed across the phonological and semantic training regimes. A comparison of each patient's ACM relative to standard image templates indicated that patient DM had moderate damage to the dorsal pathway that was restricted to more posterior portions of the tract, associated with the more perceptual aspects of speech processing (Vandermosten et al., 2012). For JS, the analysis revealed more severe damage to the dorsal pathway at the intersection of the anterior and longitudinal segment, with the anterior segment associated with fluent speech (Fridriksson, Guo, Fillmore, Holland, & Rorden, 2013) and the longitudinal segment associated with auditory memory for pseudowords (López-Barroso et al., 2013). Hence the patients differed in both the extent and location of disrupted connectivity along the dorsal pathway. In terms of whether a differing preference of semantic versus phonological training is related to the patients' underlying damage, given both DM and JS showed effectively equivalent improvements on trained items from the two different relearning strategies, this indicates that both therapies aimed at the damaged and the intact pathways can produce appreciable improvements for trained items.

While both DM and JS showed a benefit for both relearning strategies on trained items, they clearly differed in terms of generalisation to the control items, and this seems to be where the most interesting picture lies in terms of relating neural damage to relearning outcomes. DM showed generalisation only after phonological training, which was significantly greater than that seen for JS both immediately and one week later. This suggests that DM's milder damage to the dorsal pathway has left him with a phonological system that can support generalisation. The implication is that for milder dorsal damage, the most appropriate treatment method would seem to be to administer restitutive phonological therapy. This aligns with proposals that when damage is less severe, aiming therapy at the damaged system is superior (Coelho, et al., 2000; Fridriksson, et al., 2009; Louis, et al., 2001; Nettleton & Lesser, 1991; Yampolsky & Wayers, 2002).

In contrast, JS showed significant generalisation only after semantic training, and this was marginally significantly greater than that seen for DM immediately, although not so at follow-up. Given that JS has more severe damage to his dorsal route, and hence his phonological system, it would seem that his more seriously damaged system cannot support generalisation. Hence the implication of the results for JS is that for more severe damage, it is worth exploring the potential of compensatory therapy directed at the relatively more intact processing systems to maximise gains to untreated items. Consistent with Ska et al.'s (2003) and Beeson et al.'s (2011) success with aiming therapy at the intact processing systems, it would appear that once the phonological system is damaged too extensively, aiming therapy at the semantic system may be more effective. Although there was evidence of some damage to JS's ventral pathway in terms of the integrity of the external capsule, this was far less than the damage to the arcuate fasciculus of the dorsal pathway. It is interesting to note that semantic therapy did not produce significant generalisation for DM despite his relatively intact ventral pathway. While there was some evidence of very localised damage to the external capsule n DM, this was much less than that observed for JS, hence we would have expected to see if anything greater gains from semantic therapy for DM than JS on the basis of ventral pathway integrity, yet the opposite was the case. This may have arisen because DM was already drawing heavily on his semantic processing to support performance, and this may not have been sufficient to support the longer and more phonologically challenging items that formed his training sets. Although we did try to match across patients on the nature of the training stimuli, there was some unavoidable variation, and indeed Fridriksson (2009) has suggested that better treatment outcomes could potentially be achieved if the treatment were tailored to the individual patients.

It is particularly important that the differential benefits of phonological and semantic training we observed were seen in terms of generalisation to untrained items. Generalisation is arguably is the most desired outcome of therapy, and our results suggest that the location and severity of the underlying neural disruption could influence the extent to which this is achieved: generalisation was obtained for restitutive phonological therapy in the case of milder dorsal damage and for compensatory semantic therapy in the case of more severe dorsal damage. Our results do not imply that a more extensive and/or intensive semantic/phonological intervention could not have produced generalisation for DM/JS. Yet within the parameters of the short and simple intervention we used in this study, it seems clear that an exclusive focus a single therapeutic approach (semantic for DM or phonological for JS) would have meant that gains could not have been made past the items focused on in therapy, and as such therapy would be slower and less efficient. Indeed, it has been suggested that in treatment studies, if improvements are only seen for the items that are specifically trained, this is a very limited treatment effect and could be considered a disappointing outcome (Franklin, 1997). To hypothesise about the mechanisms behind this generalisation, in the phonological condition, generalisation could be achieved due to the fact that trained phonemes may occur in the untrained words. In the semantic treatment, generalisation could be caused by the paradigm encouraging people to adopt a more general semantic processing strategy.

We have interpreted the key difference between DM and JS in terms of the location and extent of the damage to components of the arcuate fasciculus in their dorsal speech processing pathway. Although both patients showed some disruption to the external capsule of the ventral processing pathway, this was stronger for JS than DM, and hence could not have explained the differential generalisation seen for semantic therapy. It is also possible that premorbid individual variation in the relative strength of each pathway may have exerted an influence on our results. Indeed, recent work by Forkel et al. (2014) has demonstrated that connectivity along the dorsal pathway of the right hemisphere in the acute phase predicts aphasic recovery after six months. We have made the assumption of functionally equivalent right arcuate strength in DM and JS on the basis of comparison of the ACM (Figure 4A), which suggests this is not likely to be a major determinant of the differential therapeutic response we observed. However, post-lesion reorganisation is likely to have varied over DM and JS as a consequence of the differing location and extent of damage to the dorsal pathway. This could have modulated the balance of residual dorsal and ventral pathway function in a manner than might explain the differential response to therapy we observed.

Of course, the difference in location and extent of damage to the dorsal pathway also corresponded to the location of each patient's cortical lesions, and this cannot be ruled out a source of variation that may have contributed to differential therapeutic outcomes. In employing the audio-visual speech perception strategy in the phonological therapy, the goal was to stimulate the left frontal regions involved in speech production. These regions were damaged extensively in JS, yet remained relatively intact in DM, which could explain his greater generalisation from the phonological therapy. Conversely, the more posterior temporo-parietal damage in DM may have undermined input to the ventral pathway, while this region was intact in JS, which could explain his greater generalisation from the semantic therapy. Yet irrespective of whether variation in white matter connectivity or location of cortical damage underpins the differential generalisation seen in the patients we considered, the results demonstrate the relevance of neural considerations in interpreting therapeutic outcomes.

Overall, our results provide promising evidence that significant improvements in single word production can be made in a matter of six sessions, although the longevity of the effects needs to be explored. These results from such short, non-intensive, computer-based training could suggest that using these programmes at home on a regular basis may lead to improvement relatively economically, something that could be considered in the design of future aphasia treatment strategies. This could be of great benefit, because although the language deficits of aphasic individuals are debilitating and distressing for the

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patients and those who care for them (Fillingham, Sage, & Lambon Ralph, 2006), they are rarely afforded continuous therapy. Indeed, the two individuals with chronic Broca's aphasia who participated in the study have shown the potential for improvement, but they are currently not receiving any kind of therapy and have not been doing so for a number of years. The improvements we observed for these patients are particularly striking given that those with chronic nonfluent aphasia are said to achieve minimal recovery of speech production (Fridriksson, et al., 2009; Fridriksson, Morrow-Odom, Moser, Fridriksson, & Baylis, 2006). The findings of significant generalisation are especially promising given the brevity of the intervention and suggest that relatively large gains could be made for relatively little time and effort.

Our results are exciting in that they indicate the potential for use of neuroimaging data to inform speech and language therapy in chronic stroke aphasia, in line with Stinear and Ward's (2013) proposal that incorporating information from neuroimaging into the planning of rehabilitation strategies could eventually lead to the improvement of post-stroke outcomes. Of course, the current two cases can only be considered to provide suggestive and preliminary evidence, but our results indicate the need for a larger case-series study using the same crossover design. Such studies would benefit from longer follow-up periods and consideration as to whether the benefits obtained could generalise to other language tasks and also everyday communication, which of course are the ultimate goal of intervention. Studies involving larger numbers of patients with variable lesion profiles would allow quantitative analyses of the relationship between therapy gains and underlying damage, thereby establishing the role of neuroimaging in optimising therapeutic intervention.

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