The right word at the right time: Lexical retrieval treatment in primary progressive aphasia

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Declaration

I certify that

(i) The intellectual work presented in this thesis is predominantly my own original work. Parts of this work were done in collaboration as indicated in Appendices III, IV and V of this thesis, and have been presented at scientific meetings and/or submitted/accepted for publication as listed on the following page. To the best of my knowledge and belief, this thesis contains no copy or paraphrase of material previously published or written by another person, except where referenced in the text of this thesis.

(ii) The work contained in this thesis has not been submitted for the award of any other degree or qualification, with one exception. An earlier analysis of the lexical retrieval data from the three Munich participants reported in Chapter 3 was carried out by Theresa Raiser and reported in her Master of Speech Therapy Thesis entitled, *Facilitation of Word Retrieval in Primary Progressive Aphasia - Presenting Three Cases*, submitted to the Ludwig-Maximilians-Universität Munich in August 2013.

(iii) The thesis including papers is less than 40 000 words in length, excluding tables, figures, references and appendices.

(iv) Ethics approval for the research described here was obtained from the following Human Research Ethics Committees:

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- South Eastern Sydney Local Health Network Northern Sector: HREC ref 11/017, with Site Specific Approval ref 11/G/044
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- Research conducted by Theresa Raiser was approved by the Ethikkommission bei der LMU Muenchen: Projekt-Nr 038-13 (Ethics Committee of the LMU [Ludwig-Maximilians-Universität] Munich: Project No. 038-13)

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"May the favour of the Lord our God rest upon us

…establish thou the work of our hands."

Psalm 90 verse 17b.

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Abstract

Word-finding difficulty is typically an early and frustrating symptom in primary progressive aphasia (PPA). This thesis reports a case series of single case experimental design studies of word-finding treatment with 10 individuals with PPA. It examines treatment gains, maintenance of gains, and generalisation of gains to untreated items and a semi-structured interview. We observed a range of outcomes and adherence patterns under the same treatment protocol and describe disease and participant factors associated with these outcomes. The thesis also presents resources to assist with clinical decision-making about the suitability of lexical retrieval treatment for individuals with PPA.

Summary

Primary progressive aphasia (PPA) is general term for progressive language impairment in the context of early preservation of non-linguistic cognition, caused by frontotemporal lobar degeneration or Alzheimer's disease. Word-finding difficulty is typically an early and frustrating symptom, prompting investigations of lexical retrieval treatment to determine factors associated with treatment gains and the maintenance and generalisation of those gains.

The first section of this thesis presents empirical data from a series of single case experimental design studies. Ten individuals with heterogeneous presentations of PPA participated in lexical retrieval treatment for periods of 2 to 90 weeks using a technique called Repetition and Reading in the Presence of a Picture. Chapter 2 presents data from eight individuals with PPA: three individuals continued treatment for an extended period and made immediate gains that were maintained over six months, three were unable to continue and made marginal gains that were not well-maintained, and two made no gains with two or four weeks of treatment. There was little evidence of generalisation to untreated items. Factors associated with good versus poor outcomes are discussed. The study in Chapter 3 found immediate gains on picture naming by a further two individuals after two weeks' treatment, but there was no generalisation to retrieval of treated words in a structured interview.

The second section of the thesis presents two expert opinion papers considering how the evidence supporting lexical retrieval treatment with individuals with PPA might be applied in clinical practice. Chapter 4 demonstrates how a speech language pathologist might investigate the evidence supporting lexical retrieval treatment for people with PPA. Chapter 5 presents a critical narrative review that describes the increase in research on lexical retrieval treatment over the past decades, summarises the participants, treatment procedures, and key findings in that research, and concludes with questions a clinician might consider in deciding whether to implement or continue with lexical retrieval treatment in PPA.

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Chapter 1
Introduction

The term *primary progressive aphasia* (PPA) describes a group of heterogeneous clinical syndromes, characterised by progressive impairments in spoken and or written language processing (speech perception and comprehension, speaking, reading or writing), caused by pathologies within the frontotemporal lobar degeneration spectrum (FTLD), or by Alzheimer pathology, in brain networks subserving language (Marshall et al., 2018). Progressive aphasic syndromes were described in the work of early modern neurologists (Pick, 1892 and Serieux, 1893; cited in Rohrer et al., 2008), and were brought to more recent attention when Mesulam (1982) described six individuals with a slowly progressive aphasia in the absence of the other cognitive and behavioural impairments typical in dementia. Reviewing 63 similar published cases ten years later, Mesulam and Weintraub (1992) distinguished fluent and nonfluent subtypes of PPA. On the basis of further published cases, Mesulam (2001) proposed that distinguishing subtypes on the bases of fluency was unreliable. He proposed that the syndrome of PPA should be diagnosed when there is insidious onset and gradual progression of word-finding and/or word comprehension deficits in the absence of significant apathy, disinhibition, loss of recent memory, visual recognition deficits or sensory-motor deficits, in cases where other neurological etiologies such as stroke or tumour could be excluded. In the same period, other researchers (Hodges, Patterson, Oxbury & Funnell, 1992; Snowden, Goulding & Neary, 1989) described *semantic dementia*, a similar syndrome characterised by progressive loss of word and object comprehension, word-finding difficulties and paucity of content in spoken language that were attributed to a core progressive deficit in semantic memory.

The word-finding difficulties in PPA and semantic dementia can also be described as anomia or lexical retrieval impairments. Lexical retrieval impairments have been noted as a prominent feature in PPA since the first reports of the syndrome. In an early professional opinion paper about PPA, McNeil and Duffy (2001) commented that the initial profile of impaired language with relatively preserved memory, executive functions, insight, social functioning and self-care in PPA was strikingly similar to the typical profile seen in aphasia of non-progressive aetiology (stroke, tumour, focal brain injury etc.). They

argued that speech-language pathologists should therefore use clinical judgement to apply treatments that were appropriate in other areas of speech-language pathology practice (stroke aphasia, motor speech disorder, dysphagia), as long as such treatments were suited to the needs of the individual with PPA and consistent with the speech-language pathologist's philosophy of treatment. McNeil and Duffy (2001, p. 481) suggested that the key question was,

> "whether the patient under consideration has the motivation, financial and other (e.g. transportation) resources, level of linguistic and other cognitive mechanisms (e.g. attention and memory) and the potential for language and communication learning and maintenance necessary to support the type of treatment to be initiated".

This thesis is entitled, *The right word at the right time: Lexical retrieval treatment in primary progressive aphasia.* It will conclude that McNeil and Duffy's question is as salient today – in relation to candidacy for and expected outcomes from word retrieval treatment in PPA – as it was when they first posed it. The thesis will provide evidence for immediate treatment gains, and for maintenance of those gains with ongoing treatment, in a subset of ten individuals with PPA who participated in an empirical study of lexical retrieval treatment using a treatment described as *Repetition and Reading in the Presence of a Picture*. It will also review the wider literature on lexical retrieval treatment in PPA. The thesis will suggest there are further questions to be answered about the the relationship between treatment factors, disease factors, linguistic and cognitive factors, personal factors, and treatment outcomes in lexical retrieval treatment conducted with people with PPA.

This Introduction to the thesis will first outline the heterogeneity of the PPA syndromes and their impacts on individuals with PPA and their close others. It will then describe current progress in developing interventions for the disease entities that cause PPA, and the interest in behavioural interventions for PPA, especially treatment for lexical retrieval impairments. It will survey the outcomes of lexical retrieval treatments in PPA as represented in seven reviews of the lexical retrieval treatment research, leading to the research and clinical questions that will be addressed by this thesis. The Introduction will conclude with an overview of the subsequent chapters of the thesis.

An overview of PPA: Clinical presentations, prevalence and impacts

Three PPA variants and the rest[1]

Following Mesulam's (1982) seminal report, research on PPA accelerated in Europe and North America and many new cases were reported in the literature, with an accompanying proliferation of classification systems that added to the fluent, nonfluent and mixed PPA subtypes identified by Mesulam and Weintraub (1992). Among these were distinctions between semantic dementia and nonfluent primary progressive aphasia (Englund et al., 1994) and between frontal/temporal and behavioural/language variants of frontotemporal dementia (Hodges & Miller, 2001; McKhann et al., 2001). Other authors used syndrome labels to capture particularly striking features of individual clinical presentations, such as pure progressive aphemia (where aphemia is a severe motor speech disorder with the clinical characteristics of dysarthria and/or apraxia of speech, e.g. Cohen, Benoit, Van Eeckhout, Ducarne & Brunet, 1993) and progressive conduction aphasia (Hillis, Selnes & Gordon, 1999). To standardise the framework used to classify cases across research centres internationally, a consensus paper published by Gorno Tempini et al. in 2011 described three variants of PPA that differ in clinical and neuroimaging features. Under the consensus criteria, *nonfluent/agrammatic PPA* (nf/avPPA) was defined by effortful, halting, apraxic speech and/or agrammatic language production, accompanied by at least two of the following: impaired comprehension of syntax, spared single word comprehension, and spared object recognition. Neuroimaging shows left posterior-frontal/insular abnormalities. *Semantic variant PPA* (svPPA), still widely known as semantic dementia (Snowden et al. 1989, Hodges et al., 1992), was defined by impaired confrontation naming and single word comprehension, as well as three of the following: impaired object knowledge, surface dyslexia or surface dysgraphia, spared repetition and spared grammatical and motor aspects of speech production. Neuroimaging shows a characteristic anterior temporal pattern of atrophy that is particularly evident in coronal scans (Van der Flier & Scheltens, 2005). *Logopenic variant PPA* (lvPPA) was defined by impaired word retrieval and impaired repetition of sentences and phrases, as well as three of the following: phonological errors in speech production, spared single word comprehension, spared motor speech skills and no frank agrammatism. Neuroimaging abnormalities are predominantly seen in left posterior perisylvian or parietal

[1] This subheading is appreciatively borrowed from: Sajjadi S.A., Patterson K., Arnold R. J., Watson P. C., Nestor P. J. (2012). Primary progressive aphasia: a tale of two syndromes and the rest. *Neurology, 78*,1670–1677.

areas in lvPPA.

Histopathological findings overlap across the three consensus variants, such that all three variants might be associated with FTLD-tau inclusions or transactive response DNA-binding protein of 43kDA (TDP-43) inclusions or Alzheimer-type pathology, with nf/avPPA most likely to be associated with FTLD tau, svPPA with TDP-43, and lvPPA with Alzheimer pathology (Gorno Tempini et al., 2011). These clinico-pathological associations were recently confirmed in a case series of 69 individuals with sporadic PPA (Spinelli et al., 2017). Accurate and early in vivo diagnosis of neuropathology is critical for development of pharmacological treatments (Oeckl, Steinacker, Feneberg & Otto, 2016; Spinelli et al., 2017) thus a primary aim of current FTLD/PPA research is to develop biomarkers for differential neuropathological diagnosis. At the current time, there is no effective disease-modifying treatment (Tsai & Boxer, 2016), thus early diagnosis of probable or confirmed pathlogy is also important to assist individuals with PPA, their close others, and their health care teams to anticipate likely future health care and other needs, and to optimise management throughout the disease course.

While the three variants in the consensus paper adequately classify the majority of cases, perhaps a fifth of cases do not meet consensus criteria for a specific variant. These are individuals with mild or mixed deficits, prominent written rather than spoken language impairments, or speech motor control impairments only (Leyton et al., 2011; Sajjadi et al., 2012). For example, Marshall et al. (2018) described six syndromes additional to the consensus variants seen in their PPA clinic: primary progressive apraxia of speech characterised by speech motor planning impairments only, mixed progressive aphasia with various features of other variants, progressive dynamic aphasia characterised primarily by reduced spontaneous output, progressive pure anomia in which word-finding difficulties are the primary symptom, progressive dysprosodia with predominant alterations to speech rhythm and melody, and progressive “pure” word deafness in which selective comprehension impairments are disproportionate to any hearing loss. These diverse syndromes highlight the differing constellations of symptoms that can be experienced by individuals who present in the clinic, associated with the diverse distributions of pathology that are possible within the language networks of the brain.

Further, because the disease is degenerative, the pathology increases and spreads over time, including within functional brain networks (Mesulam et al., 2014). Symptoms therefore vary over the disease course, as well as at initial presentation, and rate and pattern of decline vary across individuals (Sapolsky et al., 2011). Typically, individuals

who present with initially selective language impairments experience an increasing language disorder with additional, non-language symptoms emerging over time. Nf/avPPA may progress to include executive and/or motor symptoms with increased pathological burden in frontal regions (Karageorgiou & Miller, 2014; Kertesz, McMonagle, Blair, Davidson & Munoz, 2005). SvPPA may progress to include symptoms such as disrupted sleep, appetite and libido, emotional blunting, disinhibition, prosopagnosia, and behavioural fixations (Karageorgiou & Miller, 2014). LvPPA associated with Alzheimer-type pathology may progress to include apraxias, episodic memory deficits and visuospatial disorders over time (Marshall et al., 2018). Other individuals may present with non-language features (other cognitive, motor or behavioural impairments) in addition to salient language impairments, and decline in these cases may involve a range of cognitive domains from the onset. Variability in disease factors (symptoms, severity, and rate of decline) is one important reason why the experience of PPA varies across individuals. The experience of PPA also varies with personal and social factors.

Estimated prevalence of PPA

In the absence of a systematic epidemiological study, it is hard to reliably estimate the number of individuals impacted by PPA in Australia at the present time. Estimation methods vary and the outcomes differ wildly. One conservative estimate (Marshall et al., 2018, citing Coyle-Gilchrist et al., 2016 and Magnin et al., 2016) is that PPA prevalence is in the order of 3 per 100 000. Given an Australian population estimate of 24 945 185[2], this would suggest there are approximately 750 people currently living with PPA in Australia. A contrasting estimate is that FTLD pathology accounts for approximately 10% of pathologically-confirmed dementias, of whom 29-57% have PPA (Karageorgiou & Miller, 2014, citing Hodges, Davies, Xuereb, Kril & Halliday, 2003; Ioannidis, Konstantinopolous, Maiovis & Karacostas, 2012; Johnson et al., 2005; and Roberson et al., 2005). On this estimate, given an estimated 356 288 Australians with dementia in 2018 (Deloitte Access Economics, 2011), 35 629 of these would have dementia associated with FTLD, such that between 10 332 and 20 308 people would currently have PPA, and an additional number would have PPA associated with Alzheimer pathology. As these estimates differ by at least an order of magnitude, it is impossible to be sure where the true

[2]http://www.abs.gov.au/ausstats/abs@.nsf/0/1647509ef7e25faaca2568a900154b63?opendocument Accessed 25 May 18

figure lies. It is safe to say, however, that at least as many others in the family, social and occupational networks of people with PPA are also impacted by PPA.

Impacts of PPA on the individual with PPA, their close others, and the wider community

The personal impacts of PPA on the individual with the disease include direct consequences of the linguistic and cognitive changes, including difficulty communicating, difficulty with activities of daily living (O'Connor, Ahmed & Mioshi, 2014), and difficulty participating in life roles including parenting, working and maintaining social relationships (Morhardt, O'Hara, Zachrich, Wieneke & Rogalski, 2017). The impact of PPA also includes the legal and financial consequences of living with a degenerative disease (Kindell, Sage & Cruice, 2015), which may be magnified in the majority of individuals with PPA who have onset prior to 65 years (Karageorgiou & Miller, 2014), as they are still in their prime earning years (Galvin, Howard, Denny, Dickinson & Tatton, 2017), and may have significant financial, occupational and parenting responsibilities. The psychoemotional impacts of all the above can be profound for the individual with PPA. They may range from embarrassment, self-consciousness and frustration over communication difficulties, to worry, anxiety, and grief associated with the progressive prognosis, the actual, perceived, or anticipated burden on close others, and the relinquishment of life goals (Morhardt et al., 2017; Rutherford, 2014; Summers & Cartwright, 2016). It is unsurprising, therefore, that depression is reported by upwards of one third of pwPPA (Ruggero, 2017). There are, however, also a small number of case reports in which individuals with PPA describe the factors that help them live positively with PPA, including facing the diagnosis, support from the healthcare team, planning communication activities, faith-related practices, maintaining family and social networks, scheduling pleasant events and meaningful activities, and having a sense of control (Douglas, 2014; Summers & Cartwright, 2016; Twigg & La Fontaine, 2016).

Family caregivers and the close others of individuals with PPA are also impacted by that person's degenerative prognosis, their communication and cognitive changes, their comorbid medical conditions, and by changes in financial and social circumstances. PPA caregivers find communication increasingly difficult in advanced disease (Riedl, Last, Diehl-Schmid & Danek, 2014), and grieve the loss of their emotional connection with the person with PPA (Kindell et al., 2014; Pozzebon, Douglas & Ames, 2017). Caregivers report a loss of approximately two-thirds of household income after diagnosis with any of the FTLD variants (i.e. the progressive aphasias or behavioural variant frontotemporal dementia; Galvin et al., 2017). They experience decline in their own health and health-

related quality of life (Galvin et al., 2017), and depression is common in caregivers just as it is in individuals with PPA (Roche, 2014). Caregivers may gain satisfaction from ensuring their loved one is well-looked after, but this may come at the expense of their own self-care (Roche, 2014). Caregiver experiences can be improved with education about the effects of the disease, as well as problem-focussed coping (Mioshi, McKinnon, Savage, O'Connor, & Hodges, 2013; Roche, Croot, MacCann, Cramer & Diehl-Schmid, 2015), accepting support, and taking control (Pozzebon et al., 2017).

Interventions for PPA

The impacts of PPA described above depend on a complex interaction between psychoemotional, social and economic factors as well as the disease factors described earlier. The impacts can be different for the person with PPA and their close others. For this reason, interventions to support people with PPA and their close others need to consider individuals within their biopsychosocial context. Lubinski and Orange (2000), for example, proposed a framework for communication intervention with people with dementia that involved (i) promoting wellness, including education about dementia and promotion of physical and mental health ; (ii) maintaining communication skills, with ongoing assessment of language and other cognitive abilities to suggest areas for intervention; (iii) identifying strategies for maintaining communication as previous abilities are compromised; and (iv) identifying opportunities for and restrictions on communication, and educating the person with dementia and their caregiver about these. More recently, Morhardt and colleagues (2013) have emphasised the importance of relational-centred care that focuses on interactions between individuals with dementia and their close others. Kindell and colleagues (2015) extended the scope of this approach to include all paid care workers and agencies that provide services. Intrapersonally, it is important for the person with PPA and their close others to focus on personally meaningful activities that promote a sense of control (Robinson, 2001).

As will be discussed below, there are currently no pharmacological agents that can stop or alter the neuropathological substrate of PPA (Tsai & Boxer, 2016), thus current best practice in modifying the impacts of PPA lies with behavioural interventions (Hodges & Piguet, 2018; Rogalski & Khayum, in press). Interventions using brain stimulation are also showing early promise (Hung et al., 2017; Ronvero, Kneifel, Thiel, Probst & Chertkow, 2017; Tsapkini, Frangakis, Gomez, Davis, & Hillis, 2014); these are discussed further in Chapter 5 of the thesis.

Pharmacological interventions

Pharmacological interventions for PPA fall into two categories, symptomatic approaches to reduce behavioural, cognitive and motor symptoms as well as anxiety and low mood (Tsai & Boxer, 2016; Karageorgiou & Miller, 2014), and disease-modifying treatments that are still under development. In the former category, there is evidence for reduced stereotypical behaviour in svPPA with the selective seratonin reuptake inhibitor (SSRI) fluvoxamine, and for improved behaviour in svPPA and nf/avPPA with dextroamphetamine (Karageorgiou & Miller, 2014). Clinical trials that aimed to reduce cognitive and language symptoms using acetlycholinesterase inhibitors (rivastigmine and galantamine: Kowa, Seki, Yamamoto, Kanda, & Toda, 2012 and Kertesz et al., 2008, respectively), the N-methyl-D-aspartate (NMDA) antagonist memantine (Boxer et al., 2013), and the dopamine agonist bromocriptine (Reed, Johnson, Thompson, Weintraub & Mesulam, 2006) have not been effective. Acetlycholinesterase inhibitors and memantine might be expected to slow the cognitive decline in lvPPA when this is due to Alzheimer pathology, but there has been no large randomised clinical trial directly investigating this hypothesis (Tippett, Hillis & Tsapkini, 2015). In case studies, dextroamphetamine (McNeil, Small, Masterson & Fossett, 1995) combined with behavioural treatment did not improve performance above behavioural treatment alone for one individual with PPA. Steroid treatment (Decker & Heilman, 2008) did yield improvements for another individual with PPA after one and three months, but these returned to baseline one month after stopping treatment, in a study where placebo effects cannot be ruled out (Jokel, Graham, Rochon & Leonard, 2014). Omentum transposition therapy[3] has also been argued to slow decline in one case by promoting a range of possible neurological repair mechanisms (Shankle et al., 2009), but this has not been replicated (Tippett et al., 2015).

Recent gains in understanding the pathogenesis of FTLD are taken as cause for optimism that effective disease-modifying pharmacological treatment will be possible, utilising techniques that inhibit tau aggregation using immunotherapy, modulate the phosphorylation or actylation of tau proteins, or stabilise microtubules when tau-microtubule binding is compromised (Tsai & Boxer, 2016). Genetic therapies applicable in familial disease are also being investigated, targeting individuals with mutation on the

[3] The omentum is a membrane lining the cavity of the abdomen that contains growth factors, neurotransmitters and gangliosides, hypothesised in the study of Shankle and colleagues (2009) to have therapeutic effects when surgically transposed to the left cerebral cortex.

GRN or C9ORF72 genes (Tsai & Boxer, 2016). A cautionary note, however, is that such treatments may still be years away (Hodges & Piguet, 2018). In this context, it is essential to investigate the benefits of currently-available non-pharmacological *behavioural interventions* that can promote participation in life activities and quality of life for people with PPA across as much of the disease course as possible (Kortte & Rogalski, 2013).

Behavioural interventions

The World Health Organisation (WHO) International Classification of Functioning, Disability and Health (WHO, 2002) provides a useful framework for conceptualising the behavioural interventions available in PPA (Figure 1). It suggests there are environmental and personal factors that interact with a person's function at bodily, activity and social participation levels in the context of a specific health condition, such as PPA. Interventions can be targeted at the level of the person's body structures and functions (including cognitive processes), their activities, their social participation, their environment, and their personal factors. As noted above, interventions that will modify FTLD or Alzheimer pathologies at the level of body structure (neuronal tissue) are not yet available. A suite of alternative behavioural interventions are available, however, targeting cognitive processes underpinning language skills, communication activities, social participation, and environmental and personal factors for the person with PPA and their close others (see Nickels & Croot, 2009; 2015 for a selection of these).

The most frequently-reported behavioural interventions for individuals with PPA are *impairment-directed interventions*, targeting a range of language skills using techniques adapted from interventions for stroke aphasia, as recommended by McNeil and Duffy (2001). These have included treatments for verb morphology using gesture (Schneider, Thompson & Luring, 1996), grammatical completeness (Hameister, Nickels, Abel & Croot, 2017), receptive phonological processing (Louis et al., 2001), apraxia of speech (Henry et al., 2013), reading aloud (Snowden, Kindell, Thompson, Richardson & Neary, 2012), dysgraphia (Rapp & Glucroft, 2009), and spelling (Tsapkini et al., 2014). Among these, the most commonly-reported interventions have targeted lexical retrieval, also the focus of this thesis.

Activity-participation directed interventions have aimed to promote activities such as conversation (Kindell, Sage, Keady & Wilkinson, 2013; Wong, Anand, Chapman, Rackley & Zientz, 2009), television viewing (Cartwright & Elliot, 2009), and instrumental activities of daily living and social interaction using AAC and communication books (Cress & King, 1999; Mooney, Beale & Fried-Oken, in press; Robinson, 2001).

Interventions targeted at environmental factors have focused on education about PPA and communication strategies, communication partner training, psychosocial support, and coping skills training for communication partners (Diehl, Mayer, Förstl & Kurz, 2003; Mioshi et al., 2013; Robinson, 2001; Volkmer, 2013).

There are relatively few reports of interventions targeting personal factors for people with PPA (Ruggero, 2017), although a small literature of reports by people with PPA is emerging in which the authors share strategies for positive living (Douglas, 2014; Summers & Cartwright, 2016; Twigg & La Fontaine, 2016). All interventions need to take account of the progressive disease, with proactive anticipation of the likely future care needs (Rogers, King & Alarcon, 2000), and regular review as needs change with decline (Sapolsky et al., 2011).

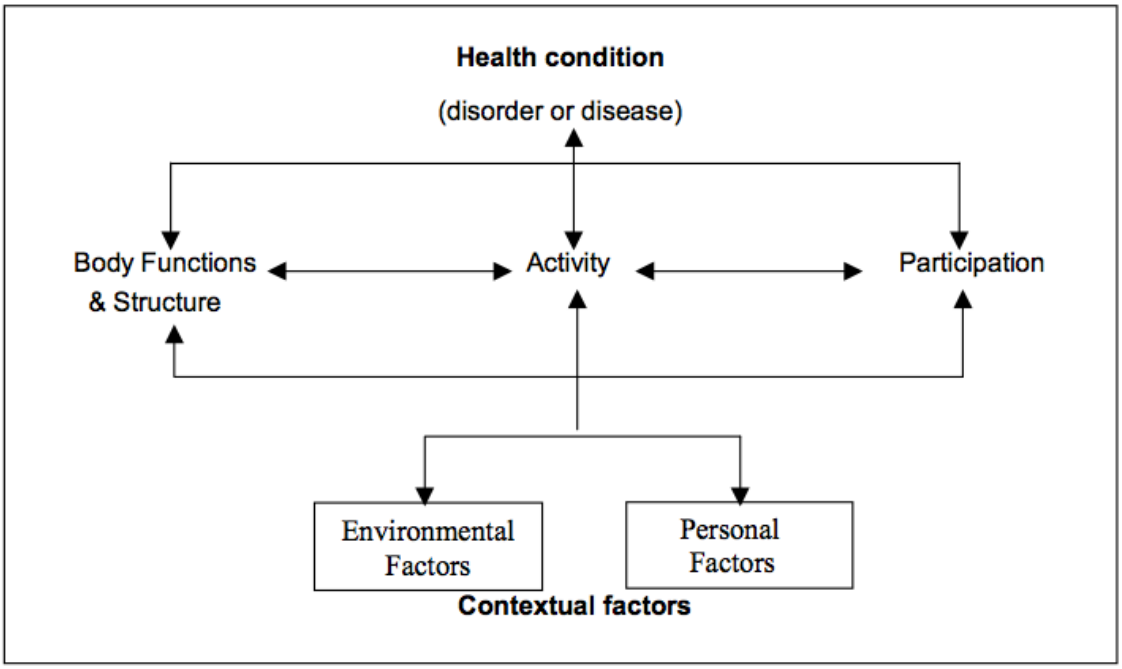

Figure 1. WHO International Classification of Functioning, Disability and Health (WHO, 2002).

Lexical retrieval treatment in PPA

Rationale for treating lexical retrieval in PPA

The majority of individuals diagnosed with PPA experience lexical retrieval difficulties in everyday communication (Mesulam, 2001). These are often of sufficient concern to lead an individual to seek a diagnosis and treatment (Rising, 2014), and may be associated with high levels of frustration for some individuals (Rohrer, 2008). This alone

might explain why such a large proportion of published intervention studies target lexical retrieval in PPA (Carthery-Goulart et al., 2013), but there are additional reasons. One is that many language and communication interventions in PPA are derived from interventions developed for individuals with aphasia due to stroke or other focal, nonprogressive brain injury as per McNeil and Duffy's advice. Intervention for word retrieval has been extensively-researched in the nonprogressive aphasia population (Nickels, 2002a, 2002b; Wisenburn & Mahoney, 2009), providing an evidence base for lexical retrieval treatment in a related clinical population before sufficient evidence was available to permit conclusions about the efficacy of lexical retrieval in PPA. Another motivation for targeting lexical retrieval processes is that lexical retrieval, for example in picture naming (Levelt, Praamstra, Meyer, Helenius & Salmelin, 1998), activates a wide network of language regions in the brain. Providing activation throughout this network may thereby support the language network as a whole. This effect may be amplified in lexical retrieval treatments that provide multimodal information about target lexical items (their semantic associations, lexical form, phonology, orthography). This widespread activation may be prophylactic in the progressive aphasias, where there is reduced activation in regions of the language network distal to the primary sites of atrophy (Mummery et al., 1999), such that promoting activation of those regions may support their function over a longer period.

Reviews of lexical retrieval intervention in PPA

A new review of the literature on lexical retrieval treatment in PPA to the end of January 2018 was conducted for this thesis (See Appendix 1) and is reported in Chapter 5. An overview this literature can be obtained from the seven published reviews of the topic that have appeared from 2008 (Henry, 2008) to the present (Beales, Cartwright & Whitworth, in press), summarised in Table 1. These reviews consider lexical retrieval treatment studies in PPA since 1995 (Funnell, 1995; McNeil et al., 1995), and in some cases also review other disorders (stroke and TBI: Casarin et al., 2014; Alzheimer's disease: Beales et al., in press). The reviewed lexical retrieval treatment studies have utilised a range of general techniques borrowed from the nonprogressive aphasia treatment literature. These include so-called standard naming treatment (Suárez-González, Savage & Caine, 2016), in which the treatment-study participant attempts to name the picture, then is given a prompt or the picture name if the attempt is not successful. Other techniques include reading and/or repeating and/or copying the picture name in the presence of the picture (Meyer, Tippett, Turner & Friedman, 2018; Savage, Piguet & Hodges, 2015),

cueing hierarchies which present a series of structured semantic and/or phonological and/or orthographic cues to assist with retrieval of the targets (e.g. Henry et al., 2013), and semantically-focused techniques that emphasise semantic features or associates of the targets (e.g. Suárez-González et al., 2016). A final technique involves eliciting treatment targets in sentences or discourse (Cartwright & Elliot, 2009; Hameister et al., 2016; Whitworth et al., 2018). The reviewed lexical retrieval treatment studies also investigate learning- and memory-related procedures such as ensuring attention during encoding (Meyer et al., 2018), expanding-interval retrieval (Bier et al., 2009), errorless versus errorful learning (Jokel & Anderson, 2012), retrieval practice (Henry et al., 2013), and consistent versus interleaved presentation of treatment targets (Hoffman, Clarke, Jones & Noonan, 2015).

The pattern of results across the reviews of these diverse treatment studies is clear in two respects. First, there is widespread support in the research literature for immediate treatment gains (also called direct treatment gains, Henry et al., 2013), and, second, these gains are likely to be lost within a two-to-six-month period following cessation of treatment for the majority of individuals. The fact that lexical retrieval improves after being treated in almost all studies, regardless of PPA variant and treatment activities, raises questions about whether any disease, participant or treatment factors are associated with better or poorer immediate gains (Jokel et al., 2014). A number of reviews recommend continuing treatment over a long period to forestall decline of treatment gains. Relatively few studies, however, investigate maintenance of treatment gains with long term treatment (Evans, Quimby, Dickey & Dickerson, 2016; Meyer et al., 2018; Reilly, 2016; Savage, et al., 2015), so the question remains as to whether this is generally good clinical advice for individuals with PPA. Regarding generalisation of treatment to untreated items, tasks and contexts, the results are far less clear. The reviews reach different conclusions about generalisation outcomes for different PPA variants, and some reviews have a generally negative outlook with regard to generalisation (e.g. Croot, Nickels, Laurence & Manning, 2009) while others make more positive claims (e.g. Beales et al., in press).

Table 1.

Summary of reviews of lexical retrieval treatment for people with primary progressive aphasia (PPA) and in some cases, people with other disorders.

Author, year	**Scope of review (publication years of reviewed studies)**	**No. studies reviewed / No. pwPPA receiving lexical retrieval treatment**	**General conclusion of review**		
			Immediate gains	**Generalisation**	**Maintenance**
Henry et al., 2008	Anomia in semantic dementia (1999-2007)	6 / 13	New learning supported by perceptual & autobiographical contextual information, spared semantic & episodic memory & phonological processing. Most benefit early in disease & on high-frequency items	svPPA: Limited because learning bound to spatiotemporal context & perceptual attributes of treatment stimuli	Continued rehearsal probably necessary to maintain gains, & may prophylactically delay loss of known items
Croot et al., 2009	Impairment & activity-parti-cipation-directed interventions in PPA (1995-2009)	26 / 13	Almost all studies show immediate gains.	Gains in naming are usually item-specific, with some reports of generalisation in nf/avPPA that may be due to learning a strategy, & one anecdotal report of transfer to conversation in a person with svPPA	Decline without ongoing treatment after 2 months to 1 year
Carthery-Goulart et al., 2013	Nonpharmacologic al interventions for cognitive impair-ment in PPA (1995-2013)	40 / 40	All studies show gains	svPPA: not to untreated items or treated stimuli in different context, with exceptions. nf/avPPA: most generalised gains to some degree to untreated items, tasks, functional communication lvPPA: generalisation to untreated items, conversation	svPPA: maintenance for variable periods after treatment. nf/avPPA & lvPPA: no general conclusion
Casarin et al., 2014	Lexical-semantic interventions in dementia, TBI, stroke (2003-2014)	28 / 18	Overall, interventions improved linguistic performance	Generalisation to untreated stimuli rarely investigated	Long-term benefits of treatment need more research

Table 1, Continued.

Summary of reviews of lexical retrieval treatment for people with primary progressive aphasia (PPA) and in some cases, people with other disorders.

Author, year	**Scope of review (publication years of reviewed studies)**	**No. studies reviewed / No. pwPPA receiving lexical retrieval treatment**	**General conclusion of review**		
			Immediate gains	**Generalisation**	**Maintenance**
Jokel et al., 2014	Lexical retrieval in PPA (1995-2013)	39 / 77	All studies show gains	svPPA: limited generalisation, to visually similar items; not to item in different context, order, or untreated items or tasks. Few reports, may not be robust. nf/avPPA: little known, potential instances may not be robust lvPPA: generalisation to untreated items in two studies	27/39 studies evaluated maintenance at 1 week to 6 months post treatment: more found gains maintained than not; treatment may prophylactically delay loss of known items
Cadorio et al., 2017	Generalisation and maintenance of treatment in PPA (2002-2015)	25 / 50	All studies show gains	svPPA: a few reports, in tasks very similar to treatment task; also overgeneralisation of new learning nf/avPPA & lvPPA: more common than in svPPA. Transfer from L2 to L1 in one lvPPA	Maintenance above baseline levels at one-to-six months post-therapy in all variants
Beales et al., in press	mechanisms of lexical retrieval & generalisation in PPA & AD (1995-2016)	37 / 52	All studies show gains except for one; another shows gains in written, but not spoken naming	26 PPA studies reported on generalisation. Approximately half of all (PPA & AD) studies show generalisation within linguistic level (e.g. from a treated to untreated word) & half across level (e.g. from a treated word to connected speech)	Not investigated

KEY: AD = Alzheimer's disease, lvPPA = logopenic variant PPA, No. = number, nf/avPPA = nonfluent/agrammatic variant PPA, PPA = primary progressive aphasia, pwPPA = people with primary progressive aphasia, svPPA = semantic variant PPA, TBI = traumatic brain injury

Approach, aims and overview of this thesis

The reviews considered above agree that given the heterogeneity of disease, participant and treatment factors across studies, it remains difficult to establish the combination(s) of factors associated with optimal immediate gains, maintenance and generalisation of gains. One approach is therefore to restrict the treatment factors and study the effects of a single treatment across a case series of diverse individuals. This approach is taken in this thesis, as well as in previous reports each describing a series of participants (e.g. Jokel et al., 2016; Reilly, 2016; Savage et al., 2015).

It remains an open question in the non-progressive aphasia literature as to whether providing the treatment target in written or spoken form for the individual with aphasia to reproduce is as effective as requiring retrieval from lexical memory (Middleton & Schwartz, 2012), and we chose the former approach for a number of reasons. First, lexical retrieval in picture naming activates a wide network of language regions in the brain (Levelt, Praamstra, Meyer, Helenius & Salmelin, 1998). This activation may be amplified in treatments such as Repetition and Reading in the Presence of a Picture that provide multimodal information about the target lexical items (semantic, in the picture; phonological, in the spoken model to be repeated; orthographic, in the written label), and may support functioning of the picture naming or wider language network in the progressive aphasias, where there is reduced activation in regions of the language network distal to the primary sites of atrophy (Mummery et al., 1999). Prophylactic effects of lexical retrieval treatment (Meyer, Tippett et al., 2016; Meyer et al., 2018; Jokel et al. 2014) may arise because promoting activation of those regions supports their function over a longer period.

Second, a Repetition and Reading in the Presence of a Picture treatment has been used successfully with semantic variant PPA (Savage, Ballard et al., 2013, Savage et al., 2014, where it was described as "Look, Listen, Repeat" treatment). Savage, Ballard, et al. (2013) compared Look, Listen, Repeat treatment with the same treatment incorporating a sentence generation task in one study and a semantic description in another, and found no advantage in lexical retrieval outcomes for either of the latter two conditions, suggesting that a range of potential cognitive mechanisms involved in sentence generation (including unprompted retrieval) or semantic elaboration did not yield additional treatment gains for the reported individuals with semantic variant PPA.

In the study reported in the present thesis, therefore, we chose to investigate lexical retrieval treatment for individuals with PPA using Repetition and Reading in the Presence of a Picture. This treatment has the advantage of being relatively simple for a person with PPA

to carry out as a home treatment, increasing the person's likely adherence to treatment, especially over the long term. Home treatment also allows for higher treatment intensity, as treatment can be undertaken every day without daily visits to the clinic. Daily treatment in turn provides distributed practice, which is likely to improve retention of learning (Middleton & Schwatz, 2012; Raymer et al., 2008). Repetition and Reading in the Presence of a Picture also provides multimodal information about the target (semantic, in the picture, phonological, in the spoken model to be repeated, and orthographic, in the written label), promoting the widespread activation within the lexical network that is hypothesised to be beneficial for the reasons described above. Finally, Repetition and Reading in the Presence of a Picture is relatively simple for the clinician to prepare, increasing the likelihood of translation of any positive results of our study to clinical practice.

Aims of the thesis

The first aim of this thesis was to investigate lexical retrieval treatment outcomes (immediate treatment gains, maintenance of treatment gains with ongoing treatment, generalisation of immediate gains on treated items to untreated items and to a semi-structured interview) using Repetition and Reading in the Presence of a Picture treatment. The participants were an unselected convenience sample of individuals with PPA drawn from working PPA clinics in Sydney, Australia, and Munich, Germany, and the design was an experimental single case series. The heterogeneous nature of the sample allowed us to observe a range of treatment outcomes and adherence patterns under the same treatment protocol, and to describe some of the disease and participant factors associated with these outcomes. The second aim of the thesis was to develop resources that can be used to support translation of knowledge about lexical retrieval treatment research in PPA into clinical practice with individuals with PPA.

Overview of the thesis

Chapters 2 and 3 describe empirical studies of lexical retrieval treatment conducted with individuals with PPA, investigating immediate treatment effects, maintenance with and without ongoing treatment, and aspects of treatment generalisation. Chapter 2 reports on a case series of eight individuals with PPA who undertook lexical retrieval treatment using Repetition and Reading in the Presence of a Picture over periods ranging from two weeks to almost two years. Chapter 3 describes two further individuals who undertook the same treatment for two weeks, and investigates whether there was any generalisation of single word treatment gains to a semi-structured interview.

Chapters 4 and 5 offer resources to assist with clinical decision-making about the suitability of lexical retrieval treatment for individuals with PPA. Chapter 4 was an invited publication in 2011 in *ACQuiring Knowledge in Speech, Language and Hearing (ACQ),* the major clinical publication of Speech Pathology Australia. It guides a hypothetical speech pathologist who is considering lexical retrieval treatment for a client with PPA through a process of evaluating the available evidence and reaching a clinical "bottom line". Chapter 5, in press in *Seminars in Speech and Language*, was solicited with the brief "to provide professionals and students with cutting-edge information that will enhance their clinical and teaching skills". It presents a review of the literature on lexical retrieval treatment in PPA to the end of January 2018, discusses whether there is any evidence that some treatments are more effective than others, and concludes with a number of questions to guide clinical decision-making about whether to implement, or continue, lexical retrieval treatment with a client with PPA. Chapter 6 summarises the main contributions of the thesis and notes some areas meriting further research. Much of the research in this thesis was undertaken collaboratively, and the contributions of co-researchers are detailed in Appendices III, IV and V.

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Chapter 2

Lexical retrieval treatment in primary progressive aphasia: An investigation of treatment duration in a heterogenous case series

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Lexical retrieval treatment in primary progressive aphasia: An investigation of treatment duration in a heterogeneous case series

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Running head: Lexical retrieval treatment in PPA

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Abstract

Word-finding difficulty is typically an early and frustrating symptom of primary progressive aphasia (PPA), prompting investigations of lexical retrieval treatment in PPA. This study investigated the effect of lexical retrieval treatment duration on immediate treatment gains, item generalisation and maintenance of gains in a single case series of eight individuals with heterogeneous PPA presentations (three non-fluent/agrammatic variant, two logopenic variant, two semantic variant, and one mixed PPA). Three individuals who continued treatment for an extended period made initial gains in picture naming and maintained them over 6 months. By contrast, three individuals who were unable to continue treatment made marginal initial gains but did not maintain them over a period of months, and two individuals did not make the typically-reported initial gains with two or four weeks of treatment. There was little evidence of generalisation to untreated items. Our results add to the evidence that daily home practice of Repetition and Reading in the Presence of a Picture over extended periods can increase and maintain retrieval of personally-relevant words in picture naming for some individuals with semantic variant PPA as well as for some individuals with nonfluent/agrammatic variant PPA. Further research is needed into the factors associated with long-term treatment adherence and gains, and the factors associated with nonadherence to treatment.

KEYWORDS: PPA, frontotemporal dementia, anomia, word retrieval, therapy

Lexical retrieval treatment in primary progressive aphasia:
An investigation of treatment duration in a heterogeneous case series

1. INTRODUCTION

The primary progressive aphasias (PPAs) are clinical syndromes associated with frontotemporal lobar degeneration or Alzheimer's disease neuropathology. They are characterised by prominent language impairments with relative sparing of other cognitive abilities in the early years post-onset. The three clinical variants recognised in a consensus paper (Gorno Tempini et al., 2011) are nonfluent/agrammatic-, semantic[1]- and logopenic-variant PPA, and there are further "mixed" cases that do not meet diagnostic criteria for these variants (Sajjadi, Patterson, Arnold, Watson & Nestor, 2012). Difficulty in word retrieval is typically an early and frustrating symptom (Mesulam, 2001), prompting investigation of lexical retrieval treatment in PPA.

A systematic review of nonpharmacological interventions for cognitive impairment in PPA (Carthery-Goulart et al., 2013) found that lexical retrieval treatments were by far the most common interventions for people with PPA (reported for 31 individuals with semantic variant PPA, 3 with nonfluent/agrammatic PPA, 2 with logopenic PPA, and 4 with PPA not classified into one of the three consensus variants). A number of other reviews (Cadório, Lousada, Martins & Figueiredo, 2017; Croot, Nickels, Laurence & Manning, 2009; Henry, Beeson & Rapcsak, 2008; Jokel, Graham, Rochon & Leonard, 2014) have concluded that the evidence for immediate treatment-related gains in retrieval of treated words, and for maintenance of these gains, is promising. There is less evidence for generalisation of treatment gains to untreated items, tasks and settings (Beales, Whitworth & Cartwright, submitted).

1.1 Immediate treatment gains

We define "immediate treatment gains" in this paper as changes in the behaviour targeted by the treatment that are attributed to the treatment (see also Croot et al., 2009); these have been described elsewhere as "direct treatment gains" (Beales, Cartwright, Whitworth & Panegyres, 2016; Henry et al., 2013). In lexical retrieval treatment, such gains are demonstrated by improvement in retrieval of treated items, typically in picture

[1] Semantic variant PPA is also widely known as semantic dementia (Hodges, Patterson, Oxbury & Funnell, 1982; Snowden, Goulding & Neary, 1988).

naming, sometimes in word generation (category fluency) tasks. Immediate treatment gains are reported in almost all published studies of lexical retrieval in PPA (Cadório et al., 2017; Carthery-Goulart et al., 2013; Croot et al., 2009; Jokel et al., 2014).

Henry et al. (2008) suggested that immediate treatment gains are a function of disease factors such as PPA subtype and severity, the associated distribution of pathology, and the residual memory and learning mechanisms. Treatment factors such as the items, language tasks and learning mechanisms targeted in treatment (Beales et al., submitted; Jokel & Anderson, 2012; Wilson, 2002), the therapy materials and activities, and the amount of practice are also likely to contribute to outcomes (Croot et al., 2009; Jokel et al., 2014). Savage, Ballard, Piguet and Hodges (2013) found that level of treatment gain was similar over three versus six weeks of treatment pairing a picture with its name and a personally-meaningful audio description for two people with semantic variant PPA, raising the intriguing possibility that increasing treatment duration may not increase treatment gain. Jokel and colleagues' (2014) critical review concluded that success was likely to be greater with personally familiar items, and that in semantic variant PPA preserved knowledge of treated items was associated with greater improvement. Nevertheless, it is not yet clear which combination of disease, participant and treatment factors are associated with optimal immediate treatment gains.

1.2 Maintenance of treatment gains

There are similar questions about which factors are associated with the maintenance of immediate treatment gains over time, with and without ongoing treatment. Our 2009 review of published behavioural interventions in PPA (Croot et al., 2009) found consistent loss of immediate treatment gains without ongoing treatment over two to twelve months following cessation of treatment activities, in the 14 studies that had investigated maintenance at that time. The one exception was an individual with semantic variant PPA whose husband reported both generalisation of treated word use to everyday conversation, and 8-month maintenance of gains without ongoing structured practice (Heredia et al., 2009). Her maintenance of gains was tentatively attributed by the researchers to the inclusion of personally meaningful definitions in treatment, her rapid learning (allowing a long period of consolidation after acquisition during the treatment period), and her ongoing use of the treated words in everyday situations after treatment. Our review recommended continuing treatment activities to maintain lexical retrieval for as long as treatment is appropriate in the context of other aspects of the individual's care, treatment goals, and life goals (Croot et al., 2009), a position also endorsed by other researchers (Cadório et al.,

2017; Jokel et al., 2014).

In the five years following 2009, the number of lexical retrieval studies investigating maintenance of treatment gains almost tripled. Jokel et al. (2014) found that approximately two thirds of the 39 studies they reviewed had investigated maintenance of treatment gains, and more than half of these reported maintenance without ongoing treatment, although some only reported maintenance over periods of a week. At present, differences in study design and participant characteristics make it difficult to determine which participant and treatment factors are reliably associated with maintenance of improvements without ongoing treatment (Carthery-Goulart et al., 2013). In the study comparing three versus six weeks' treatment, mentioned earlier, Savage, Ballard et al. (2013) found better maintenance of treatment gains after six than three weeks' practice for two people with semantic variant PPA.

Very few studies provide information about maintenance of lexical retrieval with ongoing treatment over periods of 6 to 24 months. Savage, Piguet and Hodges (2015) reported nine participants with semantic dementia whose maintenance of word retrieval in picture naming was monitored over six-months following two initial four-week periods of treatment. When naming accuracy dropped below 80% of post-treatment levels, revision practice was introduced to restore post-treatment accuracy. There were three broad outcomes: participants maintained accuracy at or above 80 per cent of words gained over the treatment period with no revision required (three participants); they required ten or fewer revision sessions over the four-month monitoring period to maintain the accuracy of words gained in treatment at or above 80% (four participants); or they required continuous revision after 2 months (two participants). Maintenance with less revision practice was associated with less severe disease, and all participants were able to maintain 80 percent or more of their treatment gains over six months with more or less revision.

Two further research groups reported stable or improved production after six months of lexical retrieval treatment (Meyer, Tippett, & Friedman, 2016; Rogalski et al., 2016). Meyer, Tippett et al. (2016) reported on six months of orthographic/phonological treatment for words that were correctly named over three baselines (prophylaxis items) and words incorrectly named over three baselines (remediation items) for groups of five people with semantic variant PPA and nine people with logopenic variant. In the orthographic treatment, participants saw the written name and picture separately and in combination for each item, and were asked to produce the name in written and spoken form and to recognise the stimulus. In the phonological treatment, the written stimuli and task were

omitted. They reported less decline on the treated prophylaxis items, consistent with the suggestion by Jokel et al. (2014) that ongoing practice would delay decline of known items. In several conditions and tasks, Meyer and colleagues also found more improvement on treated remediation items, compared with untreated item sets. Rogalski et al. (2016) offered lexical retrieval treatment (semantic, phonological and orthographic cueing) alone or in combination with motor speech treatment via an online/telemedicine platform to 21 individuals with varied PPA presentations. Around half the participants continued the treatment for 6 months, with production accuracy for this group maintained over this period.

Finally, Reilly (2016) reported the longest treatment to date for five people with semantic variant PPA, using pictures organised in semantic categories on a communication board. In 30-minute sessions approximately three times a week, a clinician gave the name of a picture, asked the participant to repeat it, then asked them to name the picture with no further cue, initiating a series of naming attempts of correctly-named items at increasing intervals to elicit spaced retrieval. The participant who was most impaired on entry to the study withdrew after 8 months, but three participants practised for 18-19 months and one for 24 months. Participants showed rapid gains, a plateau, then gradual decline.

In summary, studies investigating maintenance of treatment gains have found that maintenance over a period without treatment may be better following a longer period of treatment (Savage, Ballard et al., 2013), and that retrieval accuracy can be improved or maintained with six months of continuous treatment (Meyer, Getz, Brennan, Hu & Friedman, 2016; Meyer, Tippett et al, 2016; Rogalski et al., 2016; Reilly, 2016). The studies also offer two caveats: first, some individuals may not persist with treatment activities over the 6-month period (Reilly, 2016; Rogalski et al., 2016), and second, over a sufficiently long period, decline may become evident even with ongoing treatment (Reilly, 2016).

1.3 Generalisation of treatment gains

Studies of lexical retrieval treatment in PPA also address generalisation of treatment gains to untreated items and untreated language tasks such as sentence production, video description or semi-structured interview. The current study investigated item generalisation, which has previously been investigated in 34 reports of lexical retrieval treatment in PPA, with 48 of the 66 individuals in these reports showing no item generalisation (Croot, in prep, 2018). Item generalisation is also rare in the literature on lexical retrieval treatment following stroke (Nickels, 2002a).

Item generalisation for 18 individuals was reported in nine studies, but the statistical analysis was not included for individual participants in three of these (Jokel & Anderson, 2012; McNeil, Small, Masterson & Tepanta, 1995; Meyer, Tippett et al., 2016), and the results were statistically unreliable in three others (Newhart et al., 2009; Robinson, Druks, Hodges & Garrard, 2009; Savage, Piguet & Hodges, 2014), leaving only three of 34 reports with potentially persuasive generalisation (Beales et al., 2016; Beeson et al., 2011; Henry et al., 2013). Cadório and colleagues in their (2017) systematic review of generalisation of PPA outcomes in 25 studies recommended that future studies investigate item generalisation further. In our earlier study of two individuals with PPA undergoing the same treatment we report here, we found no generalisation to untreated words (Croot et al., 2015).

1.4 The present study

Carthery-Goulart et al. (2013) rated the quality of evidence in reports of PPA treatment in their systematic review, using criteria described by Ciccerone et al. (2000). The vast majority of studies were rated as Class III, "obtained from one or more single cases that used appropriate single-subject methods with adequate quantification and analysis of results" (Carthery-Goulart et al., 2013, p. 127). They concluded that together, the reviewed studies provided sufficient evidence to support lexical retrieval treatment as a "Practice Option"[2] in semantic variant PPA. There was insufficient investigation of lexical retrieval in nonfluent/agrammatic PPA and logopenic PPA to fully support such a recommendation, despite positive reports of treatment effects. Therefore, despite the burgeoning number of studies on lexical retrieval treatment in PPA, evidence on lexical retrieval treatment in nonfluent/agrammatic PPA and logopenic PPA is still limited (Carthery-Goulart et al., 2013). There is also a need for better understanding of factors supporting optimal immediate gains, maintenance, and generalisation of those gains (Cadório et al., 2017; Carthery-Goulart et al., 2013; Jokel et al., 2014), to inform clinical decisions about which treatments are best suited to which participants.

The present study therefore investigated immediate treatment gains on treated items, generalisation to untreated items, and maintenance of treatment gains as a function

[2] A recommendation as a "Practice Option" based on Ciccerone et al. (2000, p. 1596) means the evidence comes from Class II ("prospective cohort studies, retrospective case-controlled studies, or clinical series with well-designed controls") or Class III ("clinical series without concurrent or studies with appropriate single subject methodology"), with additional grounds to support the recommendation, although the clinical certainty is unclear.

of lexical retrieval treatment duration in PPA in a series of eight single case experimental design studies. The heterogeneous sample allowed us to observe a range of patterns in treatment adherence and outcome under the same treatment protocol. We investigated treatment utilising Repetition and Reading in the Presence of a Picture, a treatment we have previously reported with two people with PPA (one nonfluent/agrammatic PPA, one logopenic PPA; Croot et al., 2015), and that has been used successfully with semantic variant PPA (Savage, Ballard et al., 2013, 2014, who described the procedure as "Look, Listen, Repeat"). Our primary motivation was to assess the applicability of this treatment across a larger and more diverse sample of people with PPA than previously reported, contributing to the evidence for (or against) lexical retrieval treatment as a Practice Option in the different clinical variants of PPA.

1.5 Aims and hypotheses

Our first aim was to detect immediate treatment effects on picture naming of treated items in a heterogeneous sample of people with PPA as a result of home practice using Repetition and Reading in the Presence of a Picture. Our second was to compare the treatment gains evident after two weeks versus four weeks of treatment to investigate whether longer treatment resulted in greater immediate treatment gains. Savage, Ballard et al. (2013) found no difference in immediate treatment gains obtained over three- versus six-week treatment periods, suggesting that the gains had plateaued within three weeks of starting treatment. In the present study we therefore manipulated treatment duration over a shorter period than Savage, Ballard et al. (2013). Finally, we aimed to deliver a period of ongoing treatment over at least six months. We sought to investigate whether continuous treatment over the long term would maintain word retrieval gains the participants achieved in the earlier treatment periods, providing evidence for our and others' clinical recommendation in support of ongoing treatment to maintain retrieval of communicatively important vocabulary in PPA.

We hypothesised that, as typically reported, we would see immediate treatment gains for all participants, regardless of PPA variant and clinical presentation. We also hypothesised that we would see greater immediate treatment gains after four than after two weeks' treatment. Our third hypothesis was that ongoing treatment over six months would maintain the lexical retrieval gains expected at the end of two or four weeks' treatment, such that lexical retrieval would be better at the end than the beginning of the study. We were not confident that we would see item generalisation because of the relative absence of this outcome in the PPA literature, but we designed our treatment to detect item

generalisation if it should occur.

2. METHOD

The study was approved by the relevant health service and university ethics committees in Sydney and Munich, and all participants gave written informed consent in accordance with the declaration of Helsinki.

2.1 Participants

Participants were eight individuals with PPA diagnosed according to the consensus criteria reported by Gorno-Tempini et al. (2011). Five participants took part in the study in Sydney, Australia, and are referred to as S1, S2, S3, S4 and S5. Three participants took part in Munich, Germany, and are referred to as M1, M2 and M3. Three met criteria for non-fluent/agrammatic variant PPA (Participants S1, S4, S5), two for logopenic variant PPA (Participants S3, M2), two for semantic variant PPA (Participants M1, M3), and one had a mixed presentation (Participant S2). Inclusion criteria were word retrieval impairment on screening and use of English as the primary language for the Sydney participants and German as the primary language for the Munich participants. Exclusion criteria were age < 40 or > 85 years, inability to give informed consent or to complete neuropsychological screening tasks to characterise non-language cognitive function, and contraindicated medical, psychiatric, language or CNS history. Demographic details for participants are summarised in Table 1, and neuropsychological, language and mood assessment results prior to the start of the study in Tables 2 (Sydney participants) and 3 (Munich participants).

The conversational trouble and repair of three participants has previously been reported, S1 as Kerrie, S3 as Tina, and S4 as Sylvia by Taylor et al. (2014). Participant S5's participation in a study subsequent to this study has been reported by Hameister, Nickels, Abel and Croot (2017), where she is reported as ANT.

Table 1.

Demographic and disease characteristics of participants at entry to the study.

	Gender	Age (yrs)	Spouse	Educ'n (yrs)	Current/Previous Occupation	PPA variant	Years post onset	Atypical regions on brain imaging
Sydney participants								
S1	F	57	Yes	15	Business executive	Nonfluent/ agrammatic	<1	Subtle reduction in Left hemisphere volume, particularly peri-insular
S2	M	68	Yes	n/a	Business executive	Mixed	1.5	Left temporo-occipital, subtle frontal changes
S3	F	59	No	n/a	Clerical administrator	Logopenic	2.5	Left temporal, especially superior temporal, Left parietal
S4	F	72	Yes	9	Secretarial roles	Nonfluent/ agrammatic	2-3	Generalised atrophy Left > Right, bilateral hippocampal changes
S5	F	71	No	13	School principal	Nonfluent/ agrammatic	1	Left mesiotemporal, peri-insular
Munich participants								
M1	M	69	No	15	Sales manager	Semantic	18[1]	Anterior temporal, Left > Right
M2	F	64	No	11	Tax consultant	Logopenic	2	Temporoparietal, Left > Right
M3	M	59	Yes	15	Engineer	Semantic	1.5	Anterior temporal, Right > Left

1. Number of years post-onset is based on a self-reported 18-year history of word-finding difficulties (initially for only a few words). Medical referral to the Neurology Clinic in Munich noted word-finding difficulties 15 years prior to this study. In 2010 he looked up words in the dictionary when he forgot their meanings. He was well-oriented to time and place in 2013 when the study began. Yrs: years; Educ'n: Education

Table 2.

Neuropsychological and language assessment results prior to the start of the study for Sydney participants. Shading indicates impaired performance according to test cutoff for the MMSE and ACE-R (total score only), or performance below 16 %ile.

		Participant				
		S1	S2	S3	S4	S5
Cognitive Assessments						
MMSE[1] /30		26	28	25	28	29
ACE-R[2] Total /100		82	-	-	68	88
	Attention /18	18	-	-	18	18
	Memory /26	24	†reduced	-	23	25
	Fluency /14	4	-	-	3	8
	Language /26	21	-	-	14	22
	Visuospatial /16	15	-	-	10	15
Digit span[3 or 7] - Maximum Forward		5	7	6	5	4
Digit span[3] – Maximum Backward		3	-	4	3	3
Rey Complex Figure[4] - Copy		2-5 %ile	††intact	>16 %ile	≤ 1 %ile	>16 %ile
Rey Complex Figure - 3-min recall		18 %ile	†reduced	<1 %ile	4 %ile	82 %ile
Trail Making Test [5,6] - Trails A		n/a (technical fault)	Unimpaired	12%ile	19-28 %ile	29-40 %ile
Trail Making Test - Trails B		Unable to understand instructions	Unimpaired	<1 %ile	Abandoned	11-18 %ile

Letter Fluency[7] (FAS)		10%ile	Severely impaired	69%ile	10%ile	<1 %ile
Category Fluency[8] (Animals)		<2 %ile	< 1 %ile	13 %ile	<3 %ile	<1 %ile
CAT[9] Cognitive Screen (T-scores)						
	Line bisection	53	66	41	44	66
	Semantic memory	60	60	60	51	60
	Recognition memory	59	35	59	59	48
	Word fluency	56	67	70	55	57
	Gesture	68	55	60	47	60
	Arithmetic	65	65	65	65	65
Language Assessments						
Test for the Reception of Grammar-2[10]		1 %ile	3 %ile	3 %ile	<1 %ile	1 %ile
Graded Naming Test[11] /30		22	20/60 BNT[14]	4	2	24
Sydney Language Battery[12]						
	Naming /30	24	-	-	14	26
	Repetition /30	25	-	-	23	27
	Word Comprehension /30	29	-	-	21	30
	Semantic Association /30	27	-	-	17	29
CAT[9] Language Battery (T-scores)						
	Comprehension: Spoken words	65	55	61	58	60
	Comprehension: Spoken sentences	58	65	60	54	58
	Comprehension: Written words	65	55	51	47	65

	Comprehension: Written sentences	59	61	62	48	68
	Repetition: Words	60	65	57	49	65
	Repetition: Sentences	56	63	56	56	48
	Naming objects	74	50	66	59	66
Mood Assessment						
Depression Anxiety and Stress Scale[13]						
	Depression	Normal	Normal	Extremely severe	Severe	Normal
	Anxiety	Normal	Mild	Normal	Extremely severe	Normal
	Stress	Normal	Moderate	Moderate	Severe	Normal

KEY: 1. MMSE = Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975), 2. ACE-R = Addenbrooke's Cognitive Examination Revised (Mioshi, Dawson, Mitchell, Arnold, & Hodges, 2006), 3. Wechsler Adult Intelligence Scales, 4th Edition (Wechsler, 1997), 4. Rey Complex Figure Test (Meyers & Meyers, 1995), 5. Trail Making Test (Tombaugh, 2004) 6. Normative data taken from the MOANS (Steinberg, Bieliauskas, Smith, & Ivnik, 2005), 7, 8.. FAS and Animal fluency (Tombaugh, Kozak & Rees, 1999), 9. CAT=Comprehensive Aphasia Test (Swinburn, Porter, & Howard, 2005), 10. Test for Reception of Grammar Second Ed (Bishop, 2003), 11. Warrington (1997), 12. Savage, Hsieh, Leslie, Foxe, Piguet & Hodges, (2013), 13. Depression Anxiety and Stress Scale, 21-item version (Henry & Crawford, 2005), 14.Boston Naming Test (Kaplan, Goodglass & Weintraub, 2001).

† Participant S2 did not complete the ACE-R, but other episodic memory testing demonstrated poor acquisition/registration of a word list, with no recall after 20 minutes, but good recognition although there were some false positives. Slightly better performance on non-verbal material.

†† Participant S2 did not complete the RCFT, but other figure copying tasks suggested intact visuospatial and visuoconstructional abilities.

n/a = not available

Table 3.
Neuropsychological and language assessment results prior to the start of the study for the Munich participants.
*Shading indicates impaired performance according to test cutoff for results on the MMSE, LEMO Naming (total score only) and BOSU, or performance below 16 %ile. *Shading is not used to indicate impaired performance on the Stroop as no published cutoffs were available..*

	Participant		
	M1	M2	M3
Cognitive Assessments			
MMSE[1] /30	26	20	26
Digit span[2] – Maximum Forward	7	2	9
Digit span[2] – Maximum Back	6	2	6
Block span[2] – Forward	7	5	9
Block span[2] – Back	6	5	8
Word List Learning[3] (correct)	9	7	16
Word List Recall[3] (correct)	1	2	4
Word List Recognition[3] (Hits)	4	6	9
Word List Recognition[3] (Correct rejections)	9	10	10
Draw Figure[3]	10	10	11
Recall Figure[3]	8	6	4
Trail Making Test[3] – Trails A (Time/errors)	63/0	74/3	66/0
Trail Making Test[3] – Trails B (Time/errors)	189/1	202/1	154/0
Letter Fluency[4] (S)	35 %ile	4 %ile	6 %ile

Category Fluency[4] (Animals)		5 %ile	1 %ile	3 %ile
*Stroop[5] colours – Correct /100		47	36	46
*Stroop[5] words – Correct /100		64	95	69
*Stroop[5] Interference /100		14	11	34
Cognitive estimates[6] /16		9	8	7
Language Assessments				
Test for the Reception of Grammar-D[7] /21		12	11	15
Boston Naming Test[3] /15		5	7	5
LEMO Naming[8] /20 (/10 High Frequency, /10 Low Frequency)		n/a	8 (5/3)	13 (9/4)
Repeat and Point[9] – Repeat /10		8	10	10
Repeat and Point[9] – Point /10		1	8	7
BOSU[10] Errors				
	Semantic association /10	5	0	4
	Primary feature sorting /10	2	0	3
	Secondary feature sorting /10	7	2	5
	Written word sorting /10	3	2	1
	Colour sorting /10	4	0	4
Aachen Aphasia Test[11]				
	Spontaneous speech[12] /5	3,5,5,3,5,4	3,5,5,3,5,5	5.5.5.4.5.5
	Token Test, Errors /50	2	9	0

	Repetition /150	144	135	146
	Reading/Writing /90	87	89	81
	Naming /120	46	85	61
	Comprehension /120	61	97	80
Mood Assessment				
Beck Depression Inventory – II[13]		30 (severe)	17 (moderate)	10 (mild)

KEY: 1. MMSE = Mini Mental State Examination (Schmid, Ehrensperger, Berres, Beck & Monsch, 2014) 2. Härting, Markowitsch, Neufeld, Calabrese, Deisinger & Kessler (2000) 3. Schmid et al. (2014) 4. RWT= Regensburg word fluency task (Aschenbrenner, Tucha & Lange, 2001) 5. Modified Stroop (Oswald & Fleischmann, 1999; only three colours, subtest duration = 45 sec, no cutoff values available) 6. Brandt et al. (2002) 7. German version of Test for Reception of Grammar TROG-D (Fox, 2006) 8. LEMO= Lexicon model-oriented (de Bleser, 2004) 9. German modified version of English Repeat and Point Test (Hodges Martinos, Woollams, Patterson & Adlam, 2008) There are no German norms, so shading indicating impaired performance is interpreted relative to control performance on the English version of the test. 10. BOSU= Bogenhausen Semantic Investigation (Glindemann, Klintwort, Ziegler & Goldenberg, 2002) 11. Huber, Poeck, Weniger & Willmes, 1983) 12. Spontaneous speech rating categories: communication/ articulation/ automatisms/ phonological, semantic/syntactic structure. 13. Beck-Depression-Inventory – Second edition (Hautzinger, Keller & Kühner 2006).

2.2 Study Design

The treatment was designed as a series of single case experimental design studies (SCEDs) in which treatment is systematically manipulated to implement experimental control across different periods for each participant. By convention (e.g., Tate et al., 2015), no-treatment periods are designated A, so in this report A_1 indicates the pretreatment (baseline) period, A_2 indicates a post-test no-treatment period, and A_3, a period in which participants did not continue with treatment due to declining health and/or motivation. Under the same convention, intervention periods are designated B, and in this study, treatment items and durations differed across three treatment periods, B_1, B_2 and B_3.

Design of the materials is described in detail below. In brief, for each participant, stimulus items were words related to semantic categories, with categories combined into two groups of items ('topics') with an approximately equal number of items in each topic. One topic was randomly selected to be treated in Periods B_1 and B_2 and items from this topic were divided into two matched sets that were randomly allocated to treatment in Period B_1 (Set 1) or Period B_2 (Set 2). Items in the second topic formed Set 3, and these were treated, together with Sets 1 and 2, in Period B_3.

The basic treatment design (Figure 1) was as follows. During the pretreatment period (Period A_1), the participant's ability to retrieve the names of all items was sampled on three occasions each separated by two weeks. The topic for treatment was randomly selected, and items in this topic were randomly assigned to Sets 1 and 2 following the second sampling point. The third pretreatment sample was immediately followed by the first treatment period (Period B_1), during which items in Set 1 were treated for two weeks, while the matched items from the same topic in Set 2 and the items from the other topic in Set 3 served as untreated controls. Next was a post-test phase (Period A_2), during which all items were named again on two occasions separated by two weeks. This was followed by a second treatment period (Period B_2), during which items in Set 2 were treated for four weeks while items in Set 1 and Set 3 were not treated; naming of items was sampled after 2 and 4 weeks within this period. Finally, there was a third treatment period (Period B_3) during which all items (Sets 1, 2 and 3) were treated continually for 26 weeks, with a final assessment of naming of all items at the end of this period.

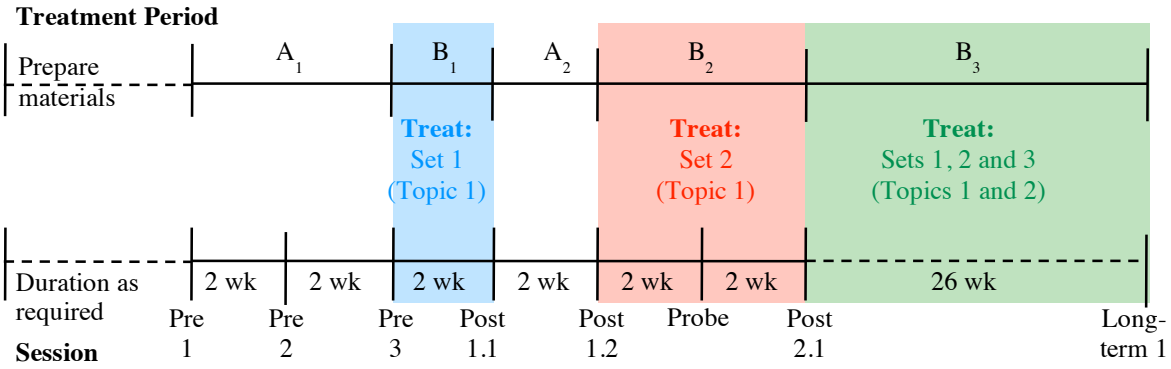


Figure 1. Intended treatment study design.

In practice, only one of the eight participants (M3) followed this design exactly; adjustments made to the intended design for all other participants are shown in Table 4. Figures illustrating the design of treatment as actually conducted for each participant are shown in Appendix 1.

Table 4.

Adjustments made to the intended design for each participant.

Participant	Adjustments to intended treatment design	Reason for adjustment
S1	Completed 1 period of treatment only, followed by one post-test (Post 1).	Rapid progression of disease prevented her continuing in study.
S2	Completed 1 period of treatment only, followed by one post-test (Post 1). Naming of all items was assessed on two later occasions, 9 and 12 weeks after Post 1, reported here as maintenance without ongoing treatment.	Participant was ill when second post-test was due, then travelled overseas. Keen to continue in study upon return but had an adverse health event.
S3	Completed 1 period of treatment only followed by two post-tests (Post 1.1 and 1.2). Naming of all items was assessed on two later occasions, 26 and 36 weeks after Post 1.2, reported here as maintenance without ongoing treatment.	Participant travelled overseas. She expressed interest in rejoining study upon return, but experienced deteriorating cognitive and mental health
M1	Completed two periods of treatment but did not adhere to treatment in third period. Longterm assessment was conducted 28 weeks after it was due.	"Obsessive" daily walking led to hospitalisation for foot injuries.
M2	Completed two periods of treatment but did not adhere to treatment in third period. Longterm assessment was conducted 9 weeks after it was due.	Reduced support from family member who previously helped her access the study.
M3	No adjustment to intended design.	Not applicable.
S4	Slight changes to intervals between sessions specified in original design.	Accommodate participants' other activities.
S5	Extended third period of treatment to 84 weeks, with naming assessed at 25, 30 and 84 weeks after Post 2.1	Participant was highly motivated to continue treatment and study participation.

Internal validity was safeguarded with opportunity for three demonstrations of the immediate treatment effect per participant, three data points in the baseline phase per participant, practitioner blinding to item treatment status, and assessor blinding to item treatment status and phase of the study. Naming accuracy was not probed repeatedly throughout each period, as naming assessment can yield improved naming (Nickels, 2002b) which would confound effects of Repetition and Reading in the Presence of the Picture. All aspects of external validity described on the 15-item Risk of Bias in N-of-1 Trials (RoBiNT) Scale (Tate et al., 2015) were addressed as recommended.

2.3 Materials

2.3.1 Experimental stimuli

The experimental stimuli were approximately 120 lexical items from personally relevant semantic categories that were individually chosen for each participant, selected on the basis of an informal conversation between the participant, spouse or frequent communication partner, and Speech Pathologist (CTR or TR) during the first week(s) of the study. Items were predominantly picturable nouns, with some proper nouns, adjectives and verbs as required, depending on participants' communication needs.

Items in their semantic categories were divided into two equal-sized groups. Related semantic categories were kept together within broad topics. For example, for Participant S2, items related to finance and travel were grouped together because they related to his previous occupation, and for Participant S5, items related to gardening and card-making were grouped together as they related to her hobbies and interests. As noted in the brief summary above, after the first two pre-test naming tests had been administered[3] (Pre 1, Pre 2), one topic was randomly allocated to be treated in the first two treatment periods B_1 and B_2 (Topic 1), and items in that topic were randomly allocated to one of two sets, Sets 1 and 2 (approximately 30 items per set), to be treated in the first and second treatment period. The approximately 60 items in the other topic (Topic 2) were treated in the third treatment period, and are henceforth described as Set 3. Sets 1 and 2 were matched on naming accuracy and error types, as well as target log spoken word frequency and log total word frequency (from CELEX; Baayen, Piepenbrock, & van Rijn, 1993), number of words (as the set included some compounds and adjective-noun combinations for example, lifeguard, Malabar Rock Pool and Great Wall of China for Participant S4), number of syllables, phonemes and letters,

[3] Pretreatment 3 was conducted immediately prior to the therapy materials being provided thus could not be included in the matching.

number of items presented with a definition/cue (see below), and number of items within a category within a set (for example, there were an equivalent number of items related to finance (Yen, budget, stock market) and travel (Qantas, suitcase, airport) within each of Sets 1 and 2 for Participant S2). There was no attempt to match materials across participants, nor to match topics within participant, apart from attempting to find items within categories that were communicatively important to the participants. See Appendix 2 for semantic categories in each set and number of items per set per participant.

2.3.2 Materials for home practice

In Periods B_1 and B_2, participants were given five PowerPoint presentation files, each containing all treatment items in the set to be practised in that period (n = approximately 30 per participant), in 5 different random orders to prevent rote learning (Graham, Patterson, Pratt, & Hodges, 1999). They were asked to practise one set per day on each weekday, and thus undertake five practice sessions per week.

In Period B_3, participants were given 20 PowerPoint files numbered one to twenty, each containing approximately a quarter of the items from Sets 1, 2 and 3, making approximately 30 items per file. All items for the study were contained in the first four files. Each of the remaining sets of four files contained the same items as the first set of four files, in different random orders in each file. Participants were now asked to practise each of these files in order from one to twenty, one per day on each weekday, so they practised all study items once each four practice days.

2.4 Procedures

2.4.1 Assessment of word retrieval in picture naming

Two pictures illustrating each item were sourced from the internet or from photographs taken by a member of the research team at the participant's house (e.g. photographs of relatives, specialist hobby equipment): one picture was presented during the picture naming assessments and the other in the treatment materials to ensure word retrieval was not solely based on learned word-picture associations. Each item was presented on a computer monitor for naming on all sessions, with items from different semantic categories and groups intermixed in the same random presentation order on each assessment. Item presentation order at assessment differed from any of the presentation orders in the treatment materials. The clinician (speech pathologist or psychology graduate) conducting the picture-naming assessments was blind to the treatment status of items in each period of the study. We were unable to collect name agreement data because many of the personally-relevant items would need to be judged for name agreement by people equally familiar with those

items as the participants, and collecting these data was beyond the resources available for the study. For example, Participant S5 had pictures of several different cuts of meat that she preferred to order from the butcher, “blade steak”, “round steak”, “short loin chops”, that may have had higher name agreement among age-matched controls as “meat” or “steak”. Other of Participant S5’s items referred to local people and places that could only be correctly recognised and named by others who knew those people and places).

Items that were not easily or uniquely depictable in a picture were also presented with a definition or sentence cue spoken by the clinician. For example, for Participant S3 the picture for “walking” (showing two people walking) was paired with the cue "What are these people doing?", and the picture of several coins lying on a receipt illustrating “tip,” was paired with the definition "extra money you leave for good service". Each picture was presented for 5 seconds before it was replaced by a screen that was blank apart from a central asterisk. Progress to subsequent items was self-paced and participants were permitted to name the picture after the 5 seconds had elapsed. We also conducted a structured interview with questions designed to elicit the treated items at each session, which is reported elsewhere (Croot et al., 2017).

2.4.2 Response coding

Picture naming responses were transcribed on-line and checked against video recordings by the clinician administering the picture-naming assessment. They were coded by another member of the research team who was blind to the treatment status of the items and the session in which they were elicited. Responses were coded as correct, semantically related, phonologically related, unrelated, empty of content, or “other” response type, using criteria minimally adapted from Croot et al. (2015). Correct responses were further analysed using strict, intermediate and lenient criteria, to allow future investigation of the reliability of conclusions about treatment effectiveness at different levels of sensitivity of scoring. Under the strict criterion, naming responses were scored as “Efficiently Correct” only when the target word was produced with no other response and within 5 seconds of the picture being presented. Responses were scored as “Correct” under the intermediate coding criterion where the response was correct under the strict criterion, or where the target word was produced first, even if after a 5-or-more-second delay, or where an acceptable alternative was produced (e.g. sofa/couch, jogging shoes/sneakers), or where there was an apraxic error (mispronounced segment, segregation of syllables). Finally, responses were scored as Leniently Correct when the target item or an acceptable synonym was produced at any time during the response, including after a circumlocution, self-cue or self-correction.

2.4.3 Treatment

Treatment was conducted using Repetition and/or Reading in the Presence of the Picture (Croot et al., 2015; Savage, Piguet & Hodges, 2015). Each item being treated was presented one at a time in pictorial, written and spoken form using PowerPoint: the second depiction of the target, that had not been used in the naming assessment, was presented for five seconds with the written name below, and an accompanying sound file containing a recording of the spoken picture name played automatically (Figure 2). Participants were asked to say the name of the picture, using the spoken and/or written form as a model. Each picture slide disappeared after 5 seconds, then participants saw a screen with a central asterisk, and could advance to the next item by pressing the space bar at their own pace. The treatment files were installed on the participants' own computer if available or they were given a laptop computer on loan for the duration of the study.

Figure 2. Illustration of participant completing treatment using Repetition and Reading in the Presence of a Picture at a home computer.
Image credits: Man at computer: iStock.com/RUSSELLTATEdotCOM modified by the first author with permission. Apple: all-free-download.com/BSGStudio

Because the speech pathologist who performed the picture naming assessments was blind to the allocation of topics and targets to treatment, the treatment materials were developed and introduced to the client by a second speech pathologist. At the first treatment session, participants were shown how to open the file and run the presentation. All subsequent treatment sessions were performed independently by the participant in their own home, with some participants receiving assistance from spouses or other relatives. In the first period of treatment they carried out the task once per day for 10 days over two weeks (five days per week). Each target item thus received five trials of therapy per week. Home treatment procedures were the same in the second (4-week) and third (long term) periods of treatment, except that in the third period, each target item was treated once every four treatment days to keep the number of items treated each day, and thus the duration of the home treatment session, constant over the course of the study.

2.4.4 Assessment of treatment adherence

Participants were asked to log their practice sessions by entering practice dates on a printed table, but logs were not given to some of the Sydney participants until later treatment periods.

2.4.5 Consistency of methods in Sydney and Munich

The Munich study was conducted as part of the requirement of a Masters Degree in Speech Pathology by the second author (TR). Fidelity of treatment and analysis methods was overseen by the first, third and final authors (KC, CT-R and LN). The second author visited Sydney for 3 months prior to commencing the study for training in treatment methods and data coding, and the first author visited Munich for 2 months during the study period and advised on participant recruitment and aspects of material and treatment design in the Munich study. Statistical analysis of all data was conducted by the first author.

2.5 Reliability

Reliability of response coding was evaluated by asking two independent speech pathologists (a native Australian English speaker and a native German speaker) experienced in coding aphasic naming responses to code 20% of responses given by each participant in each session following training in using the codes. Like the original coders, the second coders were blind to phase of the study and treatment status of the items. Cohen's kappa is a measure of inter-rater agreement in which 0 represents the amount of agreement that can be expected by chance, and 1 represents perfect agreement (McHugh, 2012). Kappa statistics were calculated for interrater reliability on response accuracy using the criteria for coding responses as Efficiently Correct or not, Correct or not, and Leniently Correct or not, across

all Australian participants (kappa = 0.96, kappa = 0.86 and kappa = 0.89 respectively) and across all German participants (kappa = 0.90, kappa = 0.92 and kappa = 0.98 respectively). Cohen (1960) suggested that kappas above 0.81 may be interpreted as showing near-perfect agreement, indicating that our coding of response accuracy under all three criteria can be considered highly reliable in this study.

2.6 Statistical analysis

Picture naming accuracy was analysed using WEighted STatistics (WEST), an approach that reduces multiple scores for an item over test points in a treatment study (i.e. assessment sessions, in the current study) to a single score using λ coefficients that determine how each score is to be weighted, avoiding the problem of autocorrelation in analysis of time series data (Howard, Best, & Nickels, 2015). We used WEST-Trend and WEST-ROC analyses to investigate immediate treatment-related improvement in the first and second treatment periods, individually and combined, as explained in Appendix 3. WEST-Trend evaluates whether there is a significant trend for improvement across baseline and treatment periods combined. WEST-ROC compares the Rate Of Change over the treatment versus the baseline periods, and allows evaluation of treatment effects even when there is instability during the baseline. Following Howard et al's (2015) conservative recommendation, we required that both the WEST-Trend and the WEST-ROC should be significant as evidence for a treatment-specific effect. The Trend and difference in Rate Of Change between baseline and treatment periods should be greater (in a positive direction) for the treated than the untreated set. We used WEST-COL (Comparison Of Levels) analyses to compare the difference in the change of level of performance from pre- to post- treatment in the second (4-week) versus the first (2-week) treatment period, and to investigate maintenance with and without ongoing treatment, also explained in Appendix 3. Weights for each analysis are given in Appendix 4: these were obtained directly from Howard et al. (2015) or using a spreadsheet to calculate these weights (Howard, personal communication). WEST-COL analyses were only used when there was no significant improvement over the baseline period; tests supporting this are reported in Appendix 5. All tests were one-tailed, and all significance levels (alphas) were set at 0.05 except where familywise Bonferroni corrections were made to protect against Type I error in multiple comparisons as described in Appendix 3.

We decided *a priori* to report performance on the "Correct" coding measure as a "middle ground" dependent variable between performance measured using the strict and the lenient coding. This measure did not penalise participants for slower but correct responses,

for naming an item with an acceptable alternative name, or for producing apraxic or dysarthric responses. Because Participant S5's accuracy coded under the Correct criterion was close to ceiling at the beginning of the study, we report her results using the stricter Efficiently Correct criterion.

3. RESULTS

3.1 Treatment adherence

Not all treatment logs were available for collection at the end of the study, but logs were collected from Participants S2, S3 and S4, and were sighted for all participants in Munich. Both Participants S2 and S3 were practising approximately 5 sets per day for the period during which they completed the logs. Participant S4 was practising both morning and evening on many days. Participant M3 was writing the words down as well as saying them aloud and practising the assigned sets more often than asked to. Participant S5 reported practising some of the non-treated items as well as all the treated items during the first and second treatment periods. Participant S5 also consistently named a number of non-target items illustrated in the photographs on each assessment session (e.g. naming "strawberries" and "cream" illustrated in the picture of the target "sponge cake"), suggesting she was also naming additional items associated with the treated items during treatment.

3.2 Picture naming results

Picture naming results are reported below according to the number of treatment periods the participants completed, concluding with a summary of results across all participants. Figures show percentages correct to allow comparison across conditions and participants, as the sets contained different numbers of items across sets and across participants (Appendix 2).

3.3 Results from Participants S1, S2 and S3 who completed one period of treatment

The proportion of pictures named correctly on each session by Participants S1, S2 and S3 who completed a two-week period of lexical retrieval treatment on Set 1, are shown in Figure 3. West-Trend and WEST-ROC analyses for these participants are summarised in Table 5 and West-COL analyses in Table 6.

3.3.1 Was there immediate treatment-related improvement in the first treatment period?

Participant S1 showed a marginally significant improvement on the treated items (Set 1), with a marginally significant positive Trend and a significant difference in the rate of improvement between the treated and untreated periods. This was marginally significantly

greater than the improvement on the matched untreated set (Set 2) which showed no significant change. These results together give marginal support for a treatment-specific effect.

Participant S2 showed a marginally significant improvement on the treated items (Set 1). However, while there was a significant difference in the Trend, there was no significant difference between the Rates of Change for the treated and matched untreated sets (Sets 1 and 2), suggesting that overall the treatment-specific effect for Participant S2 was not reliable.

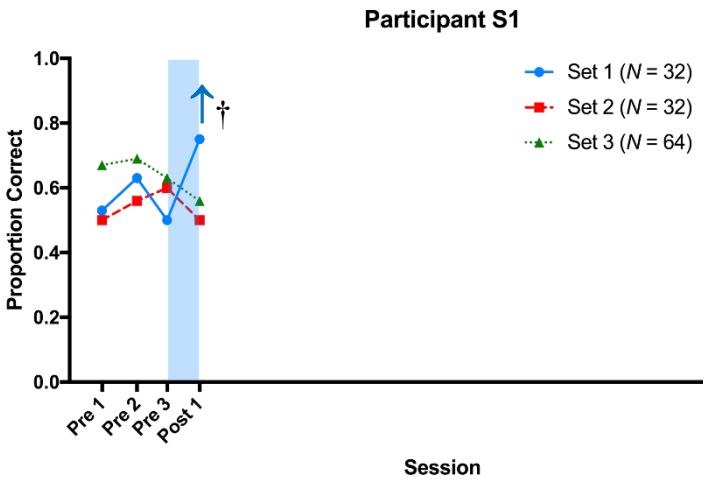
Participant S3 showed no evidence of a treatment-specific effect. Although there was significantly more improvement on the treated Set 1 in the treated period (WEST-ROC), this reflected the downward trend over baseline. This rapid decline was more likely to reflect her anxiety about the assessments than her progressive language disorder, given her otherwise relatively slow pattern of decline over the study period. There was also a marginally significant improvement on the matched untreated Set 2 in the treated period, supporting the interpretation of no treatment-specific effect for Set 1.

3.3.2 Was naming accuracy maintained after the first period of treatment?

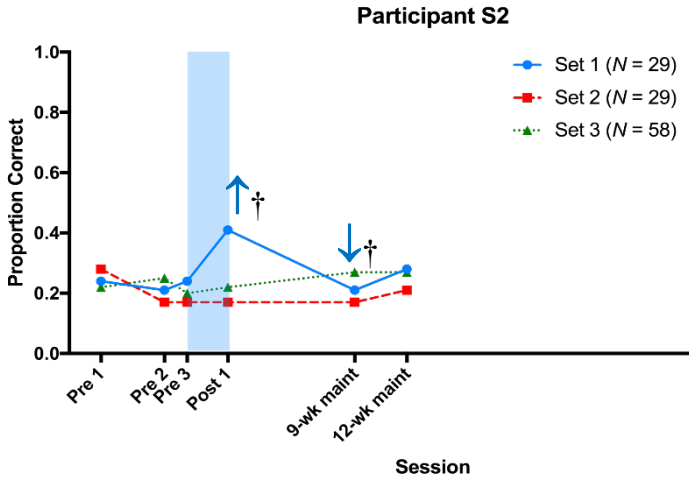
The marginal improvement by Participant S2 on the treated set showed a marginally significant decline after 9 weeks with no further treatment, although this decline was no longer statistically significant at 12 weeks post-treatment. This individual's naming accuracy was stable with no further treatment relative to the pretreatment period on all three sets.

While Participant S3's naming accuracy was maintained at 26 weeks following the end of treatment, there was a statistically significant decline by 36 weeks post-treatment on Set 3 and a marginally significant decline on Set 1. There was also a significant decline relative to pretreatment performance at 36 weeks post-treatment for the items in Set 3. Although decline on the untreated Set 3 relative to pretreatment in the absence of significant decline on the treated Set 1 could indicate a protective effect of treatment (such that treated items declined less), there was no parallel decline on the matched untreated Set 2. These results therefore do not support a prophylactic effect of treatment on naming accuracy for this individual.

a)



b)



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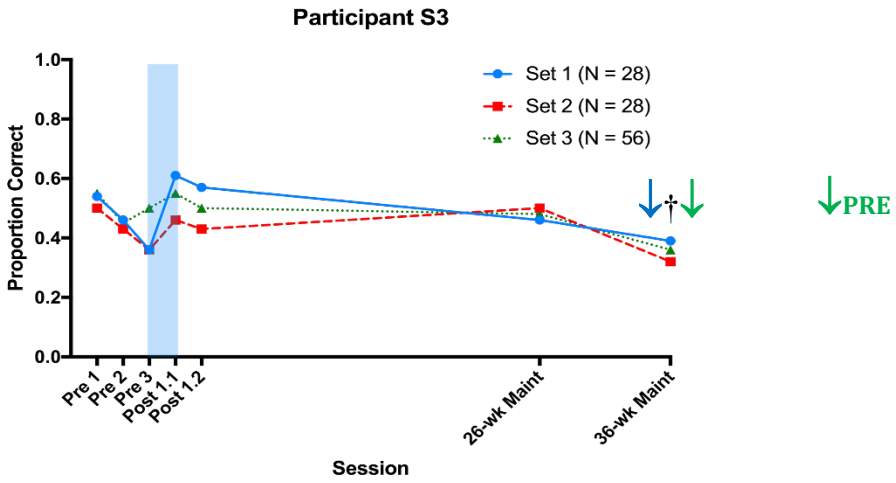


Figure 3. Proportion of pictures named correctly on each session by a) Participant S1, b) Participant S2 and c) Participant S3, who all completed a two-week period of lexical retrieval treatment on Set 1. Shading indicates the treatment period. Up/down arrows indicate significant treatment-related improvement or significant decline over the preceding period, † denotes that the effect indicated by the preceding arrow was marginal. PRE indicates improvement or decline shown by preceding arrow is relative to the pretreatment period.

Table 5.

Participants S1, S2 and S3: Analysis of treatment-specific improvement after one period of treatment.

	WEST-Trend			WEST-ROC			Treatment-specific improvement?
	t	**df**	**p**	**t**	**df**	**p**	
Participant S1							
Pre 1, Pre 2, Pre 3 & Post 1							
Set 1 (Treated)	1.61	31	0.059†	1.85	31	0.037*	**Marginal**
Set 2 (Untreated)	-0.39	31	0.650	-0.26	31	0.603	No
Set 3 (Untreated)	-2.07	63	0.979	-0.73	63	0.77	No
Set 1 vs Set 2	1.59	60	0.058†	1.68	60	0.05†	**Marginal**
Participant S2							
Pre 1, Pre 2, Pre 3 & Post 1							
Set 1 (Treated)	1.75	28	0.046*	1.56	28	0.065†	**Marginal**
Set 2 (Untreated)	-1.47	28	0.924	0.69	28	0.248	No
Set 3 (Untreated)	-0.29	58	0.612	0.139	58	0.445	No
Set 1 vs Set 2	2.27	56	0.014*	0.745	56	0.230	No
Participant S3							
Pre 1, Pre 2, Pre 3 & Post 1, Post 1.2							
Set 1 (Treated)	0.88	27	0.193	2.72	27	0.006*	No
Set 2 (Untreated)	-0.46	27	0.676	1.47	27	0.077†	No
Set 3 (Untreated)	0	55	0.5	1.15	55	0.127	No
Set 1 vs Set 2	0.96	54	0.172	0.90	54	0.187	No

KEY: All one-tailed p-values are right-tailed, except where noted to show decline, where left-tailed p-values are reported. Grey shaded cells indicate significant and marginally significant results * = significant at $\alpha = 0.05$, † = marginally significant at $\alpha = 0.1$, WEST = WEighted STatistics, ROC = Rate Of Change. 'Treatment-specific improvement' is indicated when both WEST-Trend and WEST-ROC are significant.

Table 6.

Participants S2 and S3: Analysis of maintenance of performance over periods without further treatment.

	WEST-COL						Was picture naming accuracy maintained without treatment?[1]
	t	**df**	**p**	**t**	**df**	**p**	
Participant S2	9-week maintenance			12-week maintenance			
Compared with Post 1							
Set 1 (Treated)	-1.99	28	0.028†	-1.68	28	0.052	**Marginal (9 weeks)** Yes (12 weeks)
Set 2 (Untreated)	0	28	0.500	0.57	28	0.714	Yes
Set 3 (Untreated)	0.90	58	0.815	0.83	58	0.795	Yes
All 3 Sets	-0.62	116	0.267	0	116	0.500	Yes
Compared with Pre 1, Pre 2, Pre 3							
Set 1 (Treated)	-0.28	28	0.391	0.60	28	0.722	Yes
Set 2 (Untreated)	-0.62	28	0.270	0	28	0.500	Yes
Set 3 (Untreated)	1.34	58	0.908	1.09	58	0.860	Yes
All 3 Sets	0.29	116	0.388	1.08	116	0.142	Yes
Participant S3	26-week maintenance			36-week maintenance			
Compared with Post 1.1, Post 1.2							
Set 1 (Treated)	-1.27	27	0.107	-1.95	27	0.031†	**Marginal**
Set 2 (Untreated)	0.59	27	0.721	-1.57	27	0.064	Yes
Set 3 (Untreated)	-0.66	55	0.256	-2.89	55	0.003*	**No**
All 3 Sets	-0.85	111	0.200	-3.82	111	<0.001*	**No**
Compared with Pre 1, Pre 2, Pre 3							
Set 1 (Treated)	0.13	27	0.552	-0.76	27	0.228	Yes
Set 2 (Untreated)	0.88	27	0.807	-1.22	27	0.115	Yes
Set 3 (Untreated)	-0.28	55	0.389	-2.41	55	0.010*	**No**
All 3 Sets	0.27	111	0.607	-2.72	111	0.004*	**No**

KEY: All one-tailed p-values are left-tailed. Grey shaded cells indicate significant and marginally significant results * = significant at adjusted $\alpha = 0.017$, † = marginally significant at adjusted $\alpha = 0.033$, WEST = WEighted STatistics, COL = Comparison Of Levels. 1 If performance on the final session was significantly worse when compared with the post-treatment session(s), or when compared with the pretreatment period, then naming has not been maintained and this column states 'No'. If there is no significant difference between performance on the final compared with the earlier session, then improvement has been maintained and this column states 'Yes'.

3.4 Results from Participants M1 and M2 who completed two periods of treatment

Figure 4 shows the proportion of pictures named correctly on each session by Participants M1 and M2, who completed two weeks of lexical retrieval treatment on Set 1 and four weeks on Set 2. They were then provided with all three sets but did not adhere to treatment activities throughout the full third period of treatment. The final session was conducted 54 weeks after the end of the second treatment period for Participant M1 due to a series of hospital admissions, and 35 weeks after the end of the second treatment period for Participant M2 due to scheduling difficulties. West-Trend and WEST-ROC analyses for these participants are summarised in Table 7 and West-COL analyses in Table 8.

3.4.1 Was there immediate treatment-related improvement in the two treatment periods?

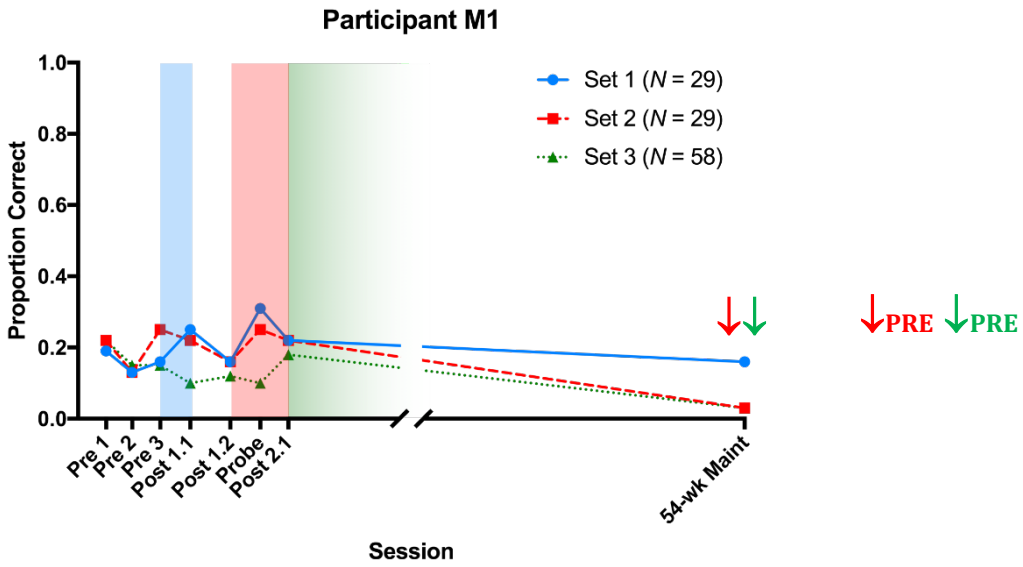
Participant M1 did not show a treatment-specific effect evidenced by significant Trend and Rate Of Change statistics for each analysis in either the first or second treatment period. Participant M2 showed improvement on items treated in the second treatment period (Set 2) that was marginally significant when using all five preceding sessions as a baseline, but there was no indication of generalisation to untreated sets.

3.4.2 Was naming accuracy maintained after the two treatment periods following nonadherence to treatment in Period 3?

Participant M1's naming of pictures in Set 1 (treated in the first treatment period) did not show significant decline at his final assessment session 54 weeks after completing treatment, whereas his naming of pictures in Set 2 (treated in the second treatment period) and Set 3 (provided for treatment in the final period) had declined, relative to the end of the second treatment period and relative to the pretreatment period.

On her final session, Participant M2's naming of pictures in Sets 1 (treated in the first treatment period, provided for practice in the final period) and 3 (provided for the third period) was maintained relative to the end of the second treatment period, whereas her naming of Set 2 (treated in the second treatment period, provided for practice in the final period) had declined relative to Post 2.1 at the end of the period in which this set was treated. Naming accuracy was maintained for all sets relative to the pretreatment period.

a)



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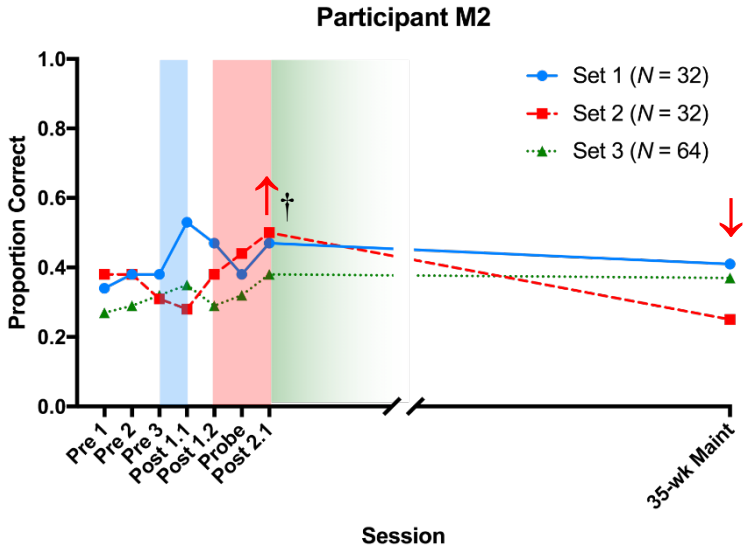


Figure 4. Proportion of pictures named correctly on each session by a) Participant M1 and b) Participant M2 who both completed a two-week lexical retrieval treatment on Set 1 and a four-week lexical retrieval treatment on Set 2, and who commenced a third period of treatment on Sets 1, 2 and 3, but did not adhere to treatment activities in the third period. First shaded area indicates the first (2-week) treatment period, second shaded area indicates the second (4-week) treatment period and the third shaded area a period in which home treatment activities commenced but were not continued. Up/down arrows indicate significant treatment-related improvement or significant decline over the preceding period, † denotes that the effect indicated by the preceding arrow was marginal. PRE indicates improvement or decline shown by preceding arrow is relative to the pretreatment period.

Table 7.
Participants M1 and M2: Analysis of treatment-specific improvement after the first and second periods of treatment.

	WEST-Trend			**WEST-ROC**			**Treatment-specific improvement?**
	t	**df**	**p**	**t**	**df**	**p**	
Participant M1							
First treatment period (Pre 1, Pre 2, Pre 3 & Post 1.1, Post 1.2)							
Set 1 (Treated)	0.37	31	0.356	1.40	31	0.086†	No
Set 2 (Untreated)	-0.37	31	0.644	-0.21	31	0.581	No
Set 3 (Untreated)	-2.12	59	0.98	-0.07	59	0.53	No
Set 1 vs Set 2	0.500	62	0.309	1.32	62	0.096†	No
Second treatment period (Post 1.1, Post 1.2, Probe, Post 2.1)							
Set 1 (Untreated)	0.32	31	0.376	1.16	31	0.127	No
Set 2 (Treated)	0.36	31	0.362	1.13	31	0.135	No
Set 3 (Untreated)	1.75	59	0.042*	0.46	59	0.322	No
Set 2 vs Set 1	0.10	62	0.462	-0.11	62	0.542	No
Second treatment period, 5 baselines (Pre 1, Pre 2, Pre 3, Post 1.1, Post 1.2, Probe, Post 2.1)							
Set 2 (Treated)	0.42	31	0.337	0.52	31	0.302	No
First and second treatment periods combined (Pre 1, Pre 2, Pre 3, Post 1.1, Post 1.2, Probe, Post 2.1)							
Sets 1 and 2 (Treated)	1.38	63	0.087†	1.07	63	0.144	No
Set 3 (Untreated)	-1.06	59	0.852	1.66	59	0.052†	No
				WEST-COL			**Greater gain in second treatment period?**
Second vs first treatment period				**t**	**df**	**p**	
Second Period Set 2 (Treated) vs First Period Set 1 (Treated)				-0.39	62	0.650	No
	WEST-Trend			**WEST-ROC**			**Treatment-specific improvement?**
	t	**df**	**p**	**t**	**df**	**p**	
Participant M2							
First treatment period (Pre 1, Pre 2, Pre 3 & Post 1.1, Post 1.2)							
Set 1 (Treated)	2.27	31	0.015*	1.28	31	0.105	No
Set 2 (Untreated)	-0.52	31	0.695	-0.09	31	0.536	No

Set 3 (Untreated)	1.06	62	0.146	0.15	62	0.439	No
Set 1 vs Set 2	1.96	62	0.027*	0.94	62	0.176	No
Second treatment period (Post 1.1, Post 1.2, Probe, Post 2.1)							
Set 1 (Untreated)	-1.01	31	0.841	1.18	31	0.12	No
Set 2 (Treated)	2.05	31	0.025*	-0.26	31	0.602	No
Set 3 (Untreated)	0.782	62	0.219	1.69	62	0.048*	No
Set 2 vs Set 1	2.23	62	0.015*	0.868	62	0.806	No
Second treatment period, 5 baselines (Pre 1, Pre 2, Pre 3, Post 1.1, Post 1.2, Probe, Post 2.1)							
Set 2 (Treated)	1.44	31	0.080†	1.74	31	0.046*	**Marginal**
First and second treatment periods combined (Pre 1, Pre 2, Pre 3, Post 1.1, Post 1.2, Probe, Post 2.1)							
Sets 1 and 2 (Treated)	1.97	63	0.027*	1	63	0.161	No
Set 3 (Untreated)	1.70	62	0.047*	0.65	62	0.259	No
				WEST-COL			**Greater gain in second treatment period?**
Second vs first treatment period				**t**	**df**	**p**	
Second Period Set 2 (Treated) vs First Period Set 1 (Treated)				-1.28	62	0.898	No

KEY: All one-tailed p-values are right-tailed. Treated/Untreated denotes the treatment status of the set during the period indicated. Grey shaded cells indicate significant and marginally significant results. * = significant at $\alpha = 0.05$, † = marginally significant at $\alpha = 0.1$. WEST = WEighted STatistics, ROC = Rate Of Change, COL = Comparison Of Levels. 'Treatment-specific improvement' is indicated when both WEST-Trend and WEST-ROC are significant.

Table 8.
Participants M1 and M2: Analysis of maintenance of performance in the third treatment period during which these participants did not adhere to treatment.

	WEST-COL			Was picture naming accuracy maintained without adherence to treatment?[1]
	t	**df**	**p**	
Participant M1				
54-week maintenance session				
Compared with Post 2.1				
Set 1 (Treated period B_1)	-1	31	0.162	Yes
Set 2 (Treated period $B_{2)}$	-2.67	31	0.006*	**No**
Set 3	-2.87	59	0.003*	**No**
All 3 Sets	-3.92	123	< 0.001*	**No**
Compared with the Pre 1, Pre 2, Pre 3				
Set 1 (Treated period B_1)	0	31	0.500	Yes
Set 2 (Treated period $B_{2)}$	-2.88	31	0.004*	**No**
Set 3	-3.486	59	< 0.001*	**No**
All 3 Sets	-3.83	123	< 0.001*	**No**
Participant M2				
35-week maintenance session				
Compared with Post 2.1				
Set 1 (Treated period B_1)	-0.81	31	0.211	Yes
Set 2 (Treated period $B_{2)}$	-2.49	31	0.009*	**No**
Set 3	-0.24	62	0.405	Yes
All 3 Sets	-1.88	126	0.031†	**Marginal**
Compared with the Pre 1, Pre 2, Pre 3				
Set 1 (Treated period B_1)	0.611	31	0.727	Yes
Set 2 (Treated period $B_{2)}$	-1.58	31	0.062	Yes
Set 3	1.44	62	0.923	Yes
All 3 Sets	0.60	126	0.723	Yes

KEY: All one-tailed p-values are left-tailed. B_1 = First treatment period, B_2 = Second treatment period. Grey shaded cells indicate significant and marginally significant results * = significant at adjusted $\alpha = 0.017$, † = marginally significant at adjusted $\alpha = 0.033$, WEST = WEighted STatistics, COL = Comparison Of Levels. 1. If performance on the final session was significantly worse when compared with the post-treatment session, or compared with the pretreatment period, then naming has not been maintained and this column states 'No'. If there is no significant difference between performance on the final compared with the earlier session, then improvement has been maintained and this column states 'Yes'.

3.5 Results from participants M3, S4 and S5 who completed three periods of treatment

The proportion of pictures named correctly on each session by Participants M3, S4 and S5 who completed two weeks of lexical retrieval treatment on Set 1, four weeks on Set 2, and a minimum of 26 weeks' treatment on all three sets are shown in Figure 5. Weighted statistics for the analyses reported in the following section are summarised in Tables 8 and 9.

3.5.1 Was there immediate treatment-related improvement in the first two treatment periods?

Participant M3 showed treatment-specific improvement on Set 1 treated in the first treatment period but not on either of the untreated sets. There was no reliable difference between the matched treated and untreated Sets 1 and 2 in this period, however, so this represents a marginal effect of treatment. Participant M3 also showed treatment-specific improvement on Set 2 treated in the second treatment period when compared with all five preceding sessions, but not with the two preceding sessions only, and no improvement on the matched untreated set. He did show a specific treatment effect for Sets 1 and 2 combined over the first two treatment periods. There was no difference in the amount of improvement for Set 2 treated for 4 weeks compared with Set 1 treated for 2 weeks.

The pattern of results was similar for Participant S4. She showed treatment-specific improvement on Set 1 treated in the first treatment period but not on either of the untreated sets. There was a reliable difference between the Rate Of Change but not the Trend comparing the matched treated and untreated Sets 1 and 2 in this period, so these results represent a marginal effect of treatment. Participant S4 did not show a reliable treatment-specific improvement on Set 2 treated in the second treatment period, and also showed no improvement on the untreated sets in the second period. She did show a specific treatment effect for Sets 1 and 2 combined over the first two treatment periods, with no reliable gain in Set 3 that was not treated over this combined period. There was no greater improvement for Set 2 treated for 4 weeks compared with Set 1 treated for 2 weeks.

A similar pattern to that seen for Participants M3 and S4 is also seen for Participant S5. She showed treatment-specific improvement on Set 1 treated in the first treatment period but not on either of the untreated sets. There was a reliable difference between the Trends but not the Rates Of Change comparing the matched treated and untreated sets (Sets 1 and 2) in this period, so these results represent a marginal effect of treatment. Participant S5 showed treatment-specific improvement on Set 2 treated in the second treatment period when compared with both two and five preceding sessions. She also showed significantly greater improvement on Set 2 versus Set 1 in this phase. It is therefore unsurprising that the treatment effects for the combined Sets 1 and 2 over the combined first two treatment periods are also

reliable. Although Participant S5 showed a marginal Trend to improvement on the untreated Set 3 in each of the first and second treatment periods, this was not significant across the two periods combined. There was no greater improvement for Set 2 treated for 4 weeks compared with Set 1 treated for 2 weeks.

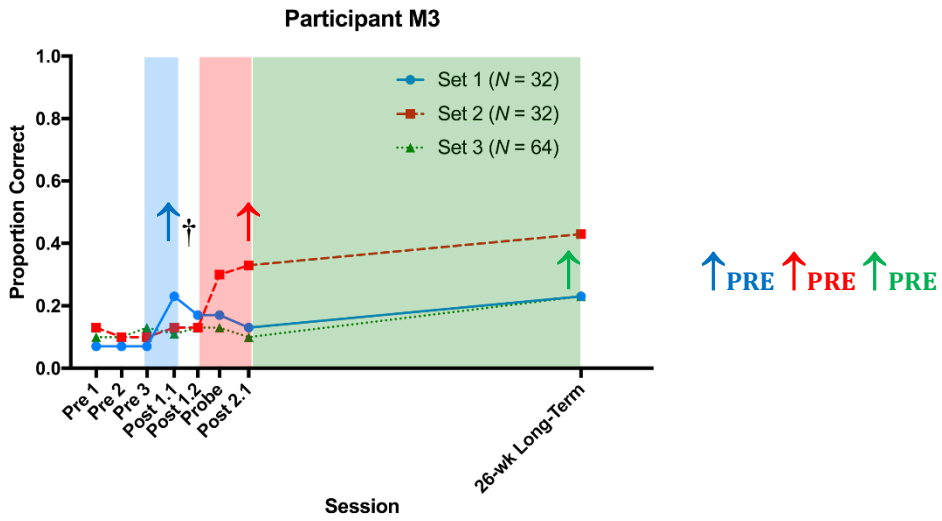
3.5.2 Was naming accuracy supported by long-term treatment?

Participant M3's picture naming was better at the end of the long-term treatment period than the end of the second treatment period for the newly-treated Set 3 and for all three sets combined. It was also better at the end of the long-term treatment period than at pretreatment for each of the sets individually and combined.

Participant S4's picture naming for the newly-treated Set 3 was better after 8 weeks of treatment and at the end of the long-term treatment period compared with the end of the second treatment period. Naming in Sets 1, 2 and all three sets combined had not improved. Participant S4's picture naming was better at the end of the long-term treatment period than at pretreatment for all three sets combined, although only Sets 1 and 3 improved reliably.

Finally, Participant S5's picture naming was not significantly better at the end of 25, 30 or 84 weeks of treatment on Sets 1, 2 or 3, or all three sets combined, compared with the end of the second treatment period. Her picture naming was, however, reliably better at each of these time points on each set individually and combined compared with pretreatment.

a)



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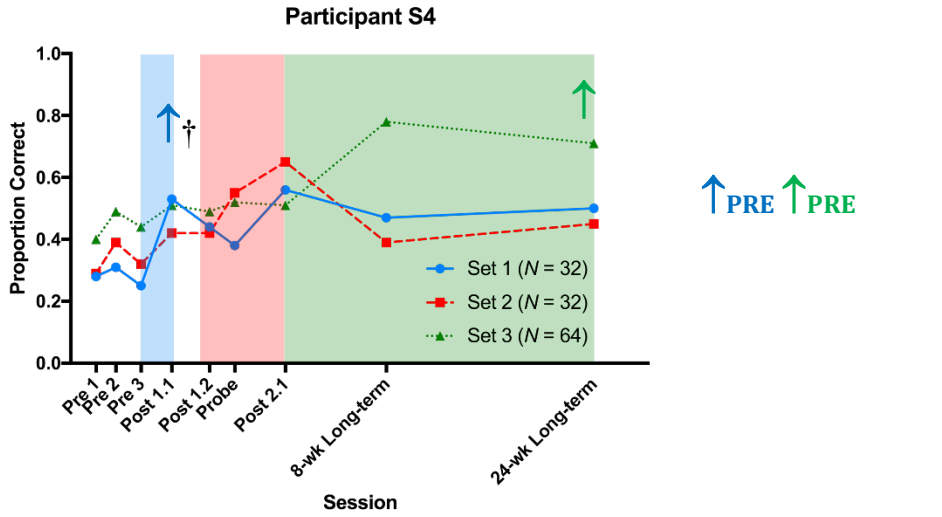

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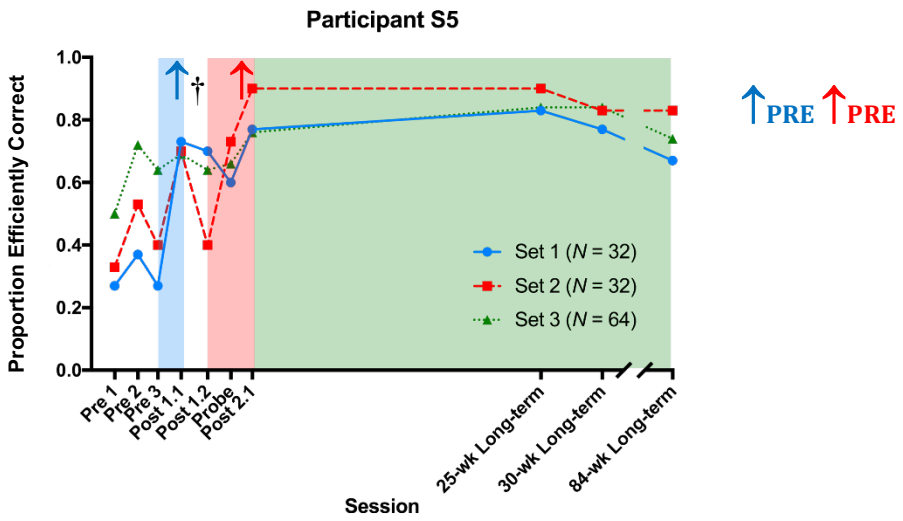

Figure 5. Proportion of pictures named correctly on each session by a) Participant M3, b) Participant S4 and c) Participant S5 who completed a two-week period of lexical retrieval treatment on Set 1, and a four-week period of lexical retrieval treatment on Set 2. All participants also completed a further period of treatment on Sets 1, 2 and 3, lasting 26 weeks for Participants M3 and S4 and 84 weeks for Participant S5. First shaded period indicates the

first (2-week) treatment period, second shaded period indicates the second (4-week) treatment period and the third shaded period the third (26 week) treatment period. Slight changes to the intervals between sessions were necessary for clinical reasons for Participant S4. Up/down arrows indicate significant treatment-related improvement or significant decline over the preceding period, † denotes that the effect indicated by the preceding arrow was marginal. PRE indicates improvement or decline shown by preceding arrow is relative to the pretreatment period.

Table 9.

Participants M3, S4 and S5: Analysis of treatment-specific improvement after the first and second periods of treatment.

	WEST-Trend			**WEST-ROC**			**Treatment-specific improvement?**
	t	**df**	**p**	**t**	**df**	**p**	
Participant M3							
First treatment period (Pre 1, Pre 2, Pre 3 & Post 1.1, Post 1.2)							
Set 1 (Treated)	2.16	29	0.019*	2.41	29	0.011*	**Yes**
Set 2 (Untreated)	0.33	29	0.373	0.93	29	0.181	No
Set 3 (Untreated)	0.90	61	0.187	-0.70	61	0.756	No
Set 1 vs Set 2	1.69	58	0.048*	1.21	58	0.115	No
Second treatment period (Post 1.1, Post 1.2, Probe, Post 2.1)							
Set 1 (Untreated)	-1.80	29	0.959	0.85	29	0.202	No
Set 2 (Treated)	2.76	29	0.005*	0.86	29	0.197	No
Set 3 (Untreated)	-0.73	61	0.764	-1.36	61	0.910	No
Set 2 vs Set 1	3.29	58	0.001*	0.32	58	0.375	No
Second treatment period, 5 baselines (Pre 1, Pre 2, Pre 3, Post 1.1, Post 1.2, Probe, Post 2.1)							
Set 2 (Treated)	2.51	29	0.009*	2.46	29	0.010*	**Yes**
First and second treatment periods combined (Pre 1, Pre 2, Pre 3, Post 1.1, Post 1.2, Probe, Post 2.1)							
Sets 1 and 2 (Treated)	2.83	59	0.003*	1.76	59	0.042*	**Yes**
Set 3 (Untreated)	0.56	61	0.288	-1.27	61	0.896	No
				WEST-COL			**Greater gain in second treatment period?**
Second vs first treatment period				**t**	**df**	**p**	
Second Period Set 2 (Treated) vs First Period Set 1 (Treated)				-0.90	58	0.813	No
	WEST-Trend			**WEST-ROC**			**Treatment-specific improvement?**
	t	**df**	**p**	**t**	**df**	**p**	
Participant S4							
First treatment period (Pre 1, Pre 2, Pre 3 & Post 1.1, Post 1.2)							
Set 1 (Treated)	1.94	31	0.031*	2.73	31	0.005*	**Yes**
Set 2 (Untreated)	1.70	30	0.05†	0.77	30	0.22	No
Set 3 (Untreated)	1.76	62	0.042*	0.43	62	0.335	No

Set 1 vs Set 2	0.73	61	0.236	1.79	61	0.039*	No
Second treatment period (Post 1.1, Post 1.2, Probe, Post 2.1)							
Set 1 (Untreated)	0.34	31	0.367	2.11	31	0.022*	No
Set 2 (Treated)	2.55	30	0.008*	0.81	30	0.213	No
Set 3 (Untreated)	0.10	62	0.459	0.150	62	0.441	No
Set 2 vs Set 1	1.62	61	0.055†	-0.88	61	0.810	No
Second treatment period, 5 baselines (Pre 1, Pre 2, Pre 3, Post 1.1, Post 1.2, Probe, Post 2.1)							
Set 2 (Treated)	3.90	30	< 0.001*	1.10	30	0.142	No
First and second treatment periods combined (Pre 1, Pre 2, Pre 3, Post 1.1, Post 1.2, Probe, Post 2.1)							
Sets 1 and 2 (Treated)	4.74	62	< 0.001*	1.70	62	0.048*	**Yes**
Set 3 (Untreated)	1.48	62	0.072†	-0.55	62	0.709	No
				WEST-COL			**Greater gain in second treatment period?**
Second vs first treatment period				**t**	**df**	**p**	
Second Period Set 2 (Treated) vs First Period Set 1 (Treated)				-1.39	61	0.915	No
Participant S5‡							
	WEST-Trend			**WEST-ROC**			**Treatment-specific improvement?**
	t	**df**	**p**	**t**	**df**	**p**	
First treatment period (Pre 1, Pre 2, Pre 3 & Post 1.1, Post 1.2)							
Set 1 (Treated)	5.18	29	< 0.000*	3.33	29	0.001*	**Yes**
Set 2 (Untreated)	1.04	29	0.153	1.400	29	0.087†	No
Set 3 (Untreated)	1.68	57	0.050†	-0.81	57	0.791	No
Set 1 vs Set 2	2.50	58	0.008*	1.12	58	0.135	No
Second treatment period (Post 1.1, Post 1.2, Probe, Post 2.1)							
Set 1 (Untreated)	0	29	0.5	0.96	29	0.172	No
Set 2 (Treated)	3.30	29	0.001*	4.46	29	< 0.001*	**Yes**
Set 3 (Untreated)	1.56	57	0.062†	1.64	57	0.054†	**Marginal**
Set 2 vs Set 1	2.43	58	0.009*	2.50	58	0.008*	**Yes**
Second treatment period, 5 baselines (Pre 1, Pre 2, Pre 3, Post 1.1, Post 1.2, Probe, Post 2.1)							
Set 2 (Treated)	4.77	29	< 0.001*	2.40	29	0.012*	**Yes**
First and second treatment periods combined (Pre 1, Pre 2, Pre 3, Post 1.1, Post 1.2, Probe, Post 2.1)							

Sets 1 and 2 (Treated)	7.01	59	< 0.001*	2.44	59	0.009*	**Yes**
Set 3 (Untreated)	2.16	57	0.018*	-0.22	57	0.585	No
				WEST-COL			**Greater gain in second treatment period?**
Second vs first treatment period				**t**	**df**	**p**	
Second Period Set 2 (Treated) vs First Period Set 1 (Treated)				-2.10	58	0.980	No

KEY: All one-tailed p-values are right-tailed. Treated/Untreated denotes the treatment status of the set during the period indicated. Grey shaded cells indicate significant and marginally significant results. * = significant at $\alpha = 0.05$, † = marginally significant at $\alpha = 0.1$. WEST = WEighted STatistics, ROC = Rate Of Change, COL = Comparison Of Levels, ‡ = Efficiently Correct responses analysed for Participant S5. 'Treatment-specific improvement' is indicated when both WEST-Trend and WEST-ROC are significant.

Table 10.

Participants M3, S4 and S5: Analysis of performance in the third treatment period during which these participants carried out continuous treatment.

Participant M3	After 26 weeks' long-term treatment											
	WEST-COL			**Is**								
	t	**df**	**p**	**retrieval better?[1]**								
Compared with Post 2.1												
Set 1 (Treated periods B_1 and B_3)	1.80	29	0.042	No								
Set 2 (Treated periods B_2 and B_3)	1.36	29	0.09	No								
Set 3 (Treated period B_3)	3.01	62	0.002*	**Yes**								
All 3 Sets	3.68	121	< 0.001*	**Yes**								
Compared with Pre 1, Pre 2, Pre 3												
Set 1 (Treated periods B_1 and B_3)	2.41	29	0.011*	**Yes**								
Set 2 (Treated periods B_2 and B_3)	3.85	29	< 0.001*	**Yes**								
Set 3 (Treated period B_3)	2.72	61	0.004*	**Yes**								
All 3 Sets	5.13	121	< 0.001*	**Yes**								
Participant S4	After 8 weeks' long-term treatment				After 24 weeks' long-term treatment							
	WEST-COL			**Is**	**WEST-COL**			**Is**				
	t	**df**	**p**	**retrieval better?[1]**	**t**	**df**	**p**	**retrieval better?[1]**				
Compared with Post 2.1												
Set 1 (Treated periods B_1 and B_3)	-1.14	31	0.868	No	-0.70	31	0.756	No				
Set 2 (Treated periods B_2 and B_3)	-2.79	30	0.996	No	-1.99	30	0.972	No				
Set 3 (Treated period B_3)	3.56	62	< 0.001*	**Yes**	2.86	62	0.003*	**Yes**				
All 3 Sets	0.90	125	0.184	No	0.78	125	0.219	No				
Compared with Pre 1, Pre 2, Pre 3												

Set 1 (Treated periods B_1 and B_3)	2.46	31	0.010*	**Yes**	2.48	31	0.009*	**Yes**				
Set 2 (Treated periods B_2 and B_3)	0.61	30	0.275	No	1.09	30	0.143	No				
Set 3 (Treated period B_3)	4.94	62	< 0.001*	**Yes**	4.19	62	< 0.001*	**Yes**				
All 3 Sets	5.00	125	< 0.001*	**Yes**	4.63	125	< 0.001*	**Yes**				
Participant S5‡	After 25 weeks' long-term treatment				After 30 weeks' long-term treatment				After 84 weeks' long-term treatment			
	WEST-COL			**Is**	**WEST-COL**			**Is**	**WEST-COL**			**Is**
	t	**df**	**p**	**retrieval better?[1]**	**t**	**df**	**p**	**retrieval better?[1]**	**t**	**df**	**p**	**retrieval better?[1]**
Compared with Post 2.1												
Set 1 (Treated periods B_1 and B_3)	1	29	0.163	No	0	29	0.500	No	-0.90	29	0.813	No
Set 2 (Treated periods B_2 and B_3)	0	29	0.500	No	-1.44	29	0.920	No	-1	29	0.837	No
Set 3 (Treated period B_3)	1.40	57	0.084	No	1.40	57	0.084	No	-0.23	57	0.590	No
All 3 Sets	1.62	117	0.054	No	0.62	117	0.267	No	-1.03	117	0.847	No
Compared with Pre 1, Pre 2, Pre 3												
Set 1 (Treated periods B_1 and B_3)	6.73	29	< 0.001*	**Yes**	4.83	29	< 0.001*	**Yes**	3.75	29	< 0.001*	**Yes**
Set 2 (Treated periods B_2 and B_3)	7.32	29	< 0.001*	**Yes**	5.18	29	< 0.001*	**Yes**	5.52	29	< 0.001*	**Yes**
Set 3 (Treated period B_3)	3.81	57	< 0.001*	**Yes**	4.06	57	< 0.001*	**Yes**	1.76	57	0.042	**No**
All 3 Sets	9.00	117	< 0.001*	**Yes**	7.82	117	< 0.001*	**Yes**	5.45	117	< 0.001*	**Yes**

KEY: All one-tailed p-values are left-tailed. B_1 = First treatment period, B_2 = Second treatment period, B_3 = Third treatment period. Grey shaded cells indicate significant and marginally significant results * = significant at adjusted $\alpha = 0.017$, † = marginally significant at adjusted $\alpha = 0.033$, ‡ = Efficiently Correct responses were analysed for Participant S5, WEST = WEighted STatistics, COL = Comparison Of Levels. 1. If performance on any session during the third treatment period was significantly better when compared with the post-treatment session, or compared with the pretreatment period, then naming has improved due to ongoing treatment during this period and this column states 'Yes. If there is no significant difference between performance on a session during Period 3 compared with the earlier session, then improvement has been maintained and this column states 'No.

3.6 Summary of Results

Immediate treatment gains and item generalisation effects for all participants over the first two treatment periods are summarised in Table 11. For the participants who completed one period of treatment, we saw marginal immediate treatment gains in picture naming on the treated set for Participants S1 and S2 but not S3, and no evidence of generalisation to untreated items. For Participants M1 and M2 who completed two periods of treatment but did not adhere to treatment throughout the third period, we saw a marginal immediate gain for Participant M2 in the second treatment period. There were no other immediate treatment gains for either participant, and there was no evidence of generalisation to untreated items. Participants M3, S4 and S5, who completed all three periods of treatment, showed marginal immediate treatment gains on Set 1 in the first treatment period and reliable gains on Sets 1 and 2 combined over the first two treatment periods. Only Participants M3 and S5 also showed reliable gains on Set 2 in the second treatment period (only in the analysis with five baseline sessions for Participant M3). There was no evidence of generalisation to untreated items for Participants M1 and S4. Participant S5 showed marginally reliable improvement on untreated items in the second treatment period, but not over both treatment periods combined. We found no evidence for a greater gain over four compared with two weeks' treatment for any of the participants who completed the first two treatment periods.

Participants' lexical retrieval outcomes at the end of the study are summarised in Table 12. Results from Participants S2 and S3 are informative about maintenance of lexical retrieval without ongoing treatment. Results from Participants M1 and M2 are only informative about maintenance without ongoing treatment with the caveat that we cannot be certain how much treatment these participants undertook on all three sets in the third treatment period before discontinuing treatment activities. While the patterns vary somewhat across sets and individuals, lexical retrieval in picture naming either remained stable or declined without ongoing treatment, relative to the end of treatment and to the beginning of the study. By contrast, lexical retrieval outcomes for Participants M3, S4 and S5 are informative about maintenance of lexical retrieval with ongoing treatment for more than six months. While the individual patterns again vary slightly, lexical retrieval was maintained or improved with ongoing treatment, relative to the end of the second treatment period and to the beginning of the study.

Table 11.

Summary of immediate treatment and generalisation effects after the first or the first and second treatment periods for all participants.

	First Treatment Period		Second Treatment Period		First and Second Treatment Periods Combined		
	Treatment-specific effect Set 1?	Generalisation to untreated sets?	Treatment-specific effect Set 2?	Generalisation to untreated sets?	Treatment-specific effect Sets 1 & 2?	Generalisation to untreated set?	Greater gain in second vs first treatment period?
Participants who completed one treatment period							
S1	**Marginal**[1]	No	-	-	-	-	-
S2	**Marginal**[1]	No	-	-	-	-	-
S3	No	No	-	-	-	-	-
Participants who completed two treatment periods but did not adhere to treatment during the third period							
M1	No	No	No	No	No	No	No
M2	No	No	**Marginal**[2]	No	No	No	No
Participants who completed three treatment periods							
M3	**Marginal**[3]	No	**Yes**[2]	No	**Yes**	No	No
S4	**Marginal**[3]	No	**Marginal**[2]	No	No	No	No
S5	**Marginal**[3]	No	**Yes**	**Marginal**	**Yes**	No	No

KEY: 1. WEST-Trend or WEST-ROC marginal for treated set, and marginal or non-significant in comparison between treated and matched untreated set. 2. WEST-Trend and WEST-ROC for treated set when 5 baselines included in the analysis. 3. WEST-Trend or WEST-ROC significant for treated set, and one non-significant in comparison between treated and matched untreated set.

Table 12.

Summary of lexical retrieval outcomes at the end of the study for all participants.

	Weeks in study	**Total weeks of treatment**	**Set/s treated**	**Lexical retrieval outcome at end of study***	
Participants who completed one period of treatment					
				Versus end of first treatment period	**Versus pretreatment period**
S1	6	2	Set 1	Not applicable: end of first treatment period was the end of the study	Set 1: Marginally improved Sets 2 & 3: Stable
S2	24	2	Set 1	Sets 1, 2 & 3: Stable	Sets 1, 2 & 3: Stable
S3	44	2	Set 1	Set 1: Marginally declined Set 2: Stable Set 3: Declined	Sets 1 & 2: Stable Set 3: Declined
				Versus end of second treatment period	**Versus pretreatment period**
Participants who completed two periods of treatment but did not adhere to treatment during the third period					
M1	68	6+	Sets 1 & 2, ? Set 3	Set 1: Stable Sets 2 & 3: Declined	Set 1: Stable Sets 2 & 3: Declined
M2	47	6+	Sets 1 & 2, ? Set 3	Set 1: Stable Set 2: Declined Set 3: Stable	Sets 1, 2 & 3: Stable
Participants who completed three periods of treatment					
M3	38	32	Sets 1, 2 & 3	Sets 1 & 2: Stable Set 3: Improved	Sets 1, 2 & 3: Improved
S4	39	32	Sets 1, 2 & 3	Sets 1 & 2: Stable Set 3: Improved	Sets 1 & 3: Improved Set 2: Stable
S5*	37	31	Sets 1, 2 & 3	Sets 1, 2 & 3: Stable	Sets 1, 2 & 3: Improved
	97	90	Sets 1, 2 & 3	Sets 1, 2 & 3: Stable	Sets 1 & 2: Improved Set 3: Stable

*Results also shown for Participant S5 at the end of the first period of long-term treatment (25 weeks' treatment of all three sets) for comparison with Participants M3 and S4, as well at the end of the study (84 weeks' treatment of all three sets).

4. DISCUSSION

This study investigated lexical retrieval treatment using Repetition and Reading in the Presence of a Picture over durations of two weeks, four weeks and more than six months in a single case series of eight individuals with heterogeneous PPA presentations. The overall aim was to contribute to the evidence for (or against) lexical retrieval treatment as a Practice Option in the different clinical variants of PPA. Our first hypothesis was that we would see immediate treatment gains for all participants, regardless of PPA variant and clinical presentation. This was not supported, as two participants did not show any evidence of treatment-specific gain. Our second hypothesis, that we would see greater immediate treatment gains after four weeks of treatment than two weeks, was also not supported for the five participants who completed the first two periods of treatment. Our third hypothesis was that ongoing treatment over six months would maintain the lexical retrieval gains expected at the end of two or four weeks' treatment, such that lexical retrieval would also be better at the end than the beginning of the study. This was supported for almost all sets treated for the three individuals who maintained treatment activities for six months or more. Finally, we did not have strong expectations of item generalisation, and, with the exception of one marginal result for Participant S5, we did not find any evidence for item generalisation.

Our results demonstrate that daily home practice of Repetition and Reading in the Presence of a Picture over six months or more can increase and maintain retrieval of personally-relevant words in picture naming for some individuals with nonfluent/agrammatic PPA and semantic variant PPA. Benefits were specific to treated words. For the individuals who did make treatment-specific gains, the single factor that best predicted maintenance of those gains was the continuation of treatment over the long-term (six months or more). These results support lexical retrieval treatment as a Practice Option for semantic variant PPA and add to the evidence for lexical retrieval treatment in nonfluent/agrammatic PPA. They also support clinical recommendations in favour of ongoing treatment to maintain treatment gains, and highlight the importance of understanding factors predicting adherence to long-term treatment.

4.1 Investigation of immediate treatment gains

The three individuals (Participants M3 with semantic variant PPA, and S4 and S5 with nonfluent agrammatic PPA) who went on to complete all three periods of treatment showed the expected immediate gains in the first two treatment periods. Two further individuals (Participants S1 and S2 with nonfluent agrammatic PPA and mixed PPA respectively) showed marginal gains on the first and only treatment period they completed

before withdrawing from the study, and one (Participant M2, semantic variant PPA) showed marginal gains, only on the second treatment period. Two others (Participants S3 and M1 with logopenic variant PPA and semantic variant PPA respectively) did not demonstrate gains.

This finding that two individuals did not demonstrate immediate treatment gains is surprising, as it is almost never reported. We used conservative criteria for determining that a treatment effect was reliable in the first two treatment periods to be certain we were identifying robust treatment gains for long-term follow-up, so we should consider whether the criteria were too conservative. Both the WEST-Trend and WEST-ROC increases had to be significant for the treated set as well as significantly greater for the treated than the matched untreated set. Consistent with these criteria, we concluded that the first treatment period gains for Participants S1 and S2 were marginal, because Participant S1 either closely approached or reached significance on all four comparisons, and Participant S2 closely approached or reached significance on three out of the four. In other words, their results were close to reliable under our criteria. By contrast, the gains for Participants S3 and M1 were far from reliable under the criteria we used to determine whether they showed a treatment-specific effect.

It was also possible that Participants S3 and M1 were not adhering to treatment during the first two treatment periods. Although both these participants self-reported good adherence to treatment, they did not have a spouse or other supporting person present each day to ensure they completed the treatment activities. A completed log was sighted for Participant M1 for the first two treatment periods, but only a partial log for Participant S3 (although this indicated that, if anything, she was doing more treatment than required). As we have noted, it was a limitation of this study that we were unable to obtain complete treatment logs for all participants, as we cannot rule out nonadherence to treatment for these two individuals. Similarly, the information we have available suggested that Participants S2, M3, S4 and S5 were carrying out more treatment than instructed, so we cannot assume that the treatment benefits were due to specifically one practice trial per item on each treatment day. Electronic treatment delivery platforms (e.g., Savage, Ballard et al., 2013; Savage et al., 2014, 2015; Rogalski et al., 2016) that collect data on how often practice materials are accessed and for how long, and that record responses, could be used to address this issue in future studies.

Another consideration is whether there are some individuals who do not benefit from lexical retrieval treatment using Repetition and Reading in the Presence of a Picture. The

conclusion that all individuals receiving impairment-directed treatment show immediate gains (Cadório et al., 2017; Carthery-Goulart et al., 2013; Croot et al., 2009; Jokel et al., 2014) may reflect a publication bias in favour of studies that show a positive effect of treatment. Interestingly, in one of the earliest lexical retrieval treatment studies (Graham et al., 1999), one participant, A.M., did not make gains on rehearsal activities similar to the ones that improved participant's D.M.'s word retrieval, although the clinical presentation and demographic features of the two individuals were similar. Graham and colleagues considered that AM's use of a phonological rather than semantic self-treatment strategy may have accounted for the difference. It is also likely be that an individual's pattern of preserved and impaired language abilities, their profile of nonlinguistic cognitive impairment (including learning and memory abilities and executive function) and other personal factors such as mood and motivation all potentially affect immediate treatment gains. Thus, a combination of disease factors (distribution and extent of pathology), language and cognitive factors, treatment factors, other participant factors, and interactions between these factors could all be associated with poor initial gains (Best & Nickels, 2000; Croot, in press). For example, in the current study, the two participants who did not make immediate treatment gains had poor episodic memory on recall measures, reduced executive function, and no spouse. Further, Participant S3 had severe anxiety and Participant M1 was up to 18 years post-onset of language symptoms and had obsessive behaviour (walking). Participant factors potentially associated with good versus poor treatment adherence and resulting outcomes in the current study are discussed further below.

4.2 Two versus four weeks of treatment

Despite our hypothesis that immediate treatment gains might be greater following four rather than two weeks' treatment, there was no advantage observed for the second treatment period for the five participants (Participants M1, M2, M3, S4 and S5) who completed both the first and second treatment periods. Although the gains in the first treatment period were marginal and those in the second more reliable for Participants M2 and S4, this difference is likely a statistical artefact due to the longer baseline analysed for the second treatment period (5 pretreatment sessions) compared with the first (3 pretreatment sessions). Indeed, when we reanalysed the data including only two pretreatment data points in the analysis, neither Participant M2 nor Participant S4 showed reliable treatment gains in the second treatment period. We can rule out the possibility that treatment duration was confounded with item difficulty in our study, as Sets 1 and 2 were matched for difficulty, and we randomly selected the topic and set that were treated first.

In other PPA studies in which gains after different durations of treatment have been described (Savage et al., 2015; Reilly, 2016), the pattern is similar to the one seen here: the immediate gains occur early in the treatment course. We found that while the immediate treatment gains may be maintained over a period of months with ongoing treatment, gains did not continue to increase over the treatment period. A number of treatment studies with individuals with semantic variant PPA (Graham et al., 1999, Savage et al., 2015) have interpreted this effect within a complementary learning systems account of new learning (McClelland, McNaughton & O'Reilly, 1995), whereby newly-learned material is initially supported by synaptic changes in the hippocampus and later consolidated to the neocortex. In semantic variant PPA, it is assumed that relatively preserved medial temporal structures can support memory for recently-experienced material but that progressive anterior temporal atrophy reduces consolidation of that material to long-term memory (Graham et al., 1999). Ongoing treatment is thought to continually support the treated items in the hippocampal memory system, consistent with the item-specific effects we observed and that were also reported by Savage et al. (2015) and Reilly (2016). The immediate treatment gains that occurred within two weeks in our study, and that were item-specific, are consistent with this account. A novel finding in the present study is that we also saw this pattern in nonfluent/agrammatic PPA (Participants S4 and S5), as well as in semantic variant PPA (Participant M3) as has been previously reported. The complementary learning systems account may extend to other PPA variants beyond semantic variant PPA, providing there is sufficient medial temporal function to support initial learning alongside reduced neocortical consolidation.

In the stroke aphasia literature, the benefit from treatments facilitating lexical access in word production has been attributed to long-term repetition priming (e.g., Nickels, 2002b, 2008). Miceli, Amitrano, Capasso, and Caramazza (1996) argue that as these tasks focus at the level of activation of individual entries in the phonological output lexicon, their effects should be item-specific — a result of ''priming'' retrieval of the phonological form. Such an account would also be consistent with our results using Repetition and Reading in the Presence of a Picture here. We assessed lexical retrieval using different pictures to those used in treatment, allowing us to conclude that the gains were not due to paired associate learning (pairing a specific picture with a verbal label) or to visual priming. Further, a priming mechanism that operates strictly on the basis of repetition priming of the phonological form would explain the lack of generalisation to untreated items. Both the complementary learning systems account and the phonological priming account suggest that

items that benefit from treatment should be produced more or less consistently across sessions, a prediction we plan to investigate in future analyses of the current results. Both accounts also predict that ongoing practice will maintain initial gains, at least until there is further disease progression.

4.3 Benefits of long-term practice

At the end of approximately six months of continuous treatment of all items (26 weeks for Participant M3, 32 weeks for Participant S4, and 30 weeks for Participant S5), lexical retrieval of previously untreated items (Set 3) was better than at the end of the second treatment period. Lexical retrieval of treated items in Sets 1 and 2 was maintained at the levels seen at the end of the second treatment period. When compared with the pretreatment period, lexical retrieval was better after approximately six months' long-term treatment for all sets for all three participants, except for Set 2 for Participant S4, which remained stable. After more than a year of further ongoing treatment of all items by Participant S5, lexical retrieval of items in Sets 1 and 2 was still better than at pretreatment, and retrieval of items in Set 3 was stable. These results for the participants who completed a long-term period of treatment in our study therefore support a recommendation of ongoing treatment for participants when this is consistent with other aspects of their clinical management.

In our results, ongoing treatment did not increase the level of initial treatment gains (which occurred in the first period of treatment for Set1, and the second period of treatment for Set 2), but did maintain those gains over at least 8 months and up to a period approaching two years. In Period B3, items were treated every fourth treatment day, rather than every treatment day as in Periods B1 and B2, to keep the number of items treated constant over the full period of the study. This was to encourage adherence to treatment, by contrast with quadrupling the number of items to be treated on each treatment day in Period B3, but it may account for the lack of further improvement on items in Sets 1 and 3 over six months' further treatment.

Our design does not allow us to determine when in the long-term treatment period the gains on Set 3 occurred. We assume, following the pattern for Sets 1 and 2, that they occurred early and then were maintained with ongoing treatment, and that there was no increased treatment response with longer treatment in the third period of treatment. Two-weekly probes during the long-term treatment period would have provided further information on this issue and the feasibility of this should be considered in future studies. Finally, while not investigated in this study, there is also evidence for the prophylactic benefits of ongoing treatment for words that can still be reliably retrieved in picture naming

(Meyer, Tippett et al., 2016).

The assumption remains that retrieval of all words is subject to decline over time in this clinical population. Given the near-universal reports of treatment gains across word retrieval treatment approaches and participants (Jokel et al., 2014; Carthery-Goulart et al., 2013), we chose not to retain a set of untreated control items over the long-term period of the study. This leaves open the possibility that the maintenance we found with ongoing treatment for Participants M3, S4 and S5 may not have differed from maintenance without ongoing treatment. Nevertheless, the first two treatment periods allowed us to investigate the specificity of the treatment effect, and we assume that the long-term period of treatment then gave Participants M1, M2, M3, S4 and S5 an opportunity to maximise the number of items benefitting from treatment. We were able to investigate maintenance without treatment for Participants S2 and S3 (at 12 weeks and 36 weeks, respectively), finding that naming was at pretreatment levels for most sets. Meyer et al. (2018) also found no maintenance of spoken naming of remediation items without ongoing treatment in a group of 8 individuals with semantic or logopenic variant PPA. In contrast, naming was above pretreatment levels for most sets at the end of 26, 24 and 84 weeks for Participants M3, S4 and S5 respectively, who conducted ongoing treatment of all three sets, treating each item once every four treatment days, over six months or more.

There can be a tension between the requirements of experimental control and the number of items made available for treatment in experimental treatment studies. Our decision was to prioritise the participant's needs over the demands of experimental control in Period B3, making all items in Set 3 available for treatment over the final treatment period. The items in this set (as for all the sets) had been selected on the basis of their functional importance to the participants. Further, our unexpected observation that some individuals were practising the treated sets more than once a day, and that Participant S5 was practising items from ostensibly untreated sets, indicate that the participants consider it in their interest to conduct as much treatment as possible.

4.4 Item generalisation

With the exception of Participant 5's marginally significant gain on untreated items in Set 3 in the second treatment period, item generalisation was not seen in the present study, consistent with the majority of PPA lexical retrieval treatment studies which have investigated item generalisation (Croot, in press). Participant S5 improved marginally on her untreated Set 3 during the second period of treatment, but improvement on this set was not statistically reliable in the first period of treatment, nor when considering the first and second

treatment periods combined. While we would welcome evidence of item generalisation as an additional outcome of treatment employing Repetition and Reading in the Presence of a Picture, we do not see strong evidence of item generalisation in Participant S5's results here Further, we are unable to entirely rule out the possibility that Participant 5 was conducting her own additional rehearsal of some items in the untreated sets. On one occasion when Participant S5 appeared to be confidently naming untreated items that had previously been frustrating her and the clinician (CTR) asked her if she had been practising extra items, she answered with an emphatic "Yes!" Participant S5's preserved episodic memory and executive function supported her in planning and list-making, which she used to manage a range of everyday activities, appointments and social behaviour (for example, sending Christmas and birthday cards, hosting dinner parties), and may also have assisted her in remembering and practising words she could not retrieve during repeated assessment sessions.

There are, nevertheless, a number of studies in the PPA lexical retrieval treatment literature that have reported item generalisation. Beeson et al. (2011) found increased generation of items in untrained categories in a word generation (category fluency) task by an individual with logopenic variant PPA. Henry et al. (2013) found improved naming of items in two untreated naming tests for one individual with logopenic variant and one with semantic variant PPA using a lexical treatment cascade procedure (although no item generalisation was found in subsequent studies using this approach; Grasso, Shuster & Henry, 2017; Kim, 2017). Beales et al. (2016) found improved naming of untreated items matched to the treated items for difficulty for all four participants in the study (one with logopenic variant and three with semantic variant PPA). All three of these studies all introduced a self-cueing strategy as well as additional memory strategies. Beeson et al.'s (2011) treatment involved multiple naming attempts of pictures presented with their written names, followed by tasks elaborating on the semantic features of the items which were later incorporated in a self-cueing strategy. This treatment also explicitly encouraged retrieval of non-target items during treatment. Henry et al. (2013) also utilised a self-cueing hierarchy involving semantic, orthographic and phonemic cues, oral reading and repetition as in our treatment here, and retrieval practice involving recall of the semantic features and the spoken and written name. Beales et al. (2016) used a self-cueing strategy that incorporated semantic, phonological, orthographic and autobiographical prompts.

Our null results together with a critical analysis of the above three studies that have found item generalisation suggest a number of factors potentially *not* be associated with item

generalisation in lexical retrieval treatment in PPA. The first is long-term treatment using Repetition and Reading in the Presence of a Picture alone: simply practising lexical retrieval over six months or more was not enough to produce item generalisation in the current study. The second is merely selecting materials in semantic categories (in our study, categories related to preferred conversational topics) without explicit semantic processing (such as the semantic plausibility judgments used by Henry et al., 2013). A third is selecting personally-relevant items without also training the ability to self-cue retrieval with the assistance of an autobiographical memory cue (as used by Beales et al. 2016). Treatment for lexical retrieval using Repetition and Reading in the Presence of a Picture is simple for participants to complete, taking approximately 10 minutes per day using one file on a home computer, but the available evidence strongly suggests that treatment effects are specific to treated items.

While our results show clear generalisation to other depictions of the treated items, we have not reported our investigation of generalisation to a connected speech task here. Participants in our study also completed semi-structured interviews designed to elicit target words in a standardised conversation, prior to and across the duration of the study period. See Chapter 3 for a description of the interview procedures. Preliminary analysis of Participant S5's data (Croot et al., 2017; see also Appendix 2) suggests that the treated words were better preserved in this conversational task than untreated words for this participant over the approximately two-year period for which we collected the interview data.

There is some evidence that repeated attempts at naming sets of words, even without success and without feedback, over time may improve lexical retrieval accuracy for that set (Nickels, 2002), although more evidence is needed (Middleton & Schwartz, 2012). We therefore considered whether conducting the semi-structured interviews to investigate generalisation to connected speech in each assessment session might have provided an unintended treatment, with the opportunity for retrieval practice being the critical ingredient (Middleton & Schwartz, 2012). However, the interviews were conducted on assessment sessions during the baselines, after the no-treatment interval in Period A2, and at long intervals (up to 6 months or more) in Period B3, whereas Repetition and Reading in the Presence of a Picture was implemented on all treatment days throughout Periods B1, B2 and B3. The logic of the study design favours changes in the treatment periods being due to Repetition and Reading in the Presence of a Picture treatment, rather than to the interviews. alone or in combination with Repetiton and Reading in the Presence of a Picture.

4.5 Participant factors associated with good versus poor adherence to treatment

In the current study, the single factor that best predicted treatment gains and

maintenance relative to the beginning of the study was the continuation of treatment activities over the long-term (six months or more). An important question, then, is which factors predict continued adherence to treatment? We have summarised a number of possible factors for each participant along with their PPA variant and information about their treatment adherence in Table 13. We considered a number of cognitive abilities (overall cognitive ability at onset of treatment as measured by a cognitive screening test, initial naming ability, initial semantic knowledge, and executive functioning over the period of the study, see also Tables 2 and 3), as well as presence of mood/anxiety disorder, and support from a spouse.

Participant S5, who maintained treatment over the longest period, was unique among the participants in the study in demonstrating all the following at entry: preserved insight into her language impairments, preserved episodic and semantic memory, executive function, and well-preserved naming on formal testing. She also reported normal mood and anxiety on a self-report questionnaire, had an excellent social network, and a high level of support from two speech pathologists. She was highly motivated to participate in treatment activities, and maintained this over the nearly two years of the study, discontinuing only to enrol in a different study (Hameister et al., 2016, in which she also made immediate treatment gains). Notably, while support from a spouse is often considered to increase treatment adherence associated with positive outcomes (Croot et al., 2009), Participant S5 did not have a spouse, but was able to organise her own treatment activities (and likely even supplement them, as discussed above).

By contrast, the two participants who did not adhere to treatment in the third period of the study had a range of cognitive impairments at the start of the study and they lived alone, relying on support from visiting family members to complete treatment activities. Participant M2 in particular was not able to continue with treatment activities after support from a family member was withdrawn. Participant M1's nonadherence to treatment activities was related to a sharp increase in what his healthcare team described as "obsessive walking" which eventually led to foot injuries and hospitalisation. Further, neither of these individuals showed a benefit of treatment in the first period of the study, and the lack of perceived or actual benefit early in treatment may have contributed to reduced engagement with treatment and eventual non-adherence. Starting treatment early in disease progression has been recommended in order to maximise the benefits of treatment (Carthery-Goulart et al., 2013), whereas Participant M1 was 18 years post-onset of symptoms.

Three participants had to withdraw from the study after only a single two-week period of treatment due to declining health. While less severe impairment is typically associated

with better treatment outcomes (Savage et al., 2015), an important factor in being able to maintain treatment activities is likely to be a slow rate of disease progression throughout the course of treatment. Participant S1 was similar to Participant S5 on entry to the study. She was within a year of onset of symptoms, with similar nonfluent/agrammatic language including notable word finding difficulties and effortful speech, in the context of excellent insight and otherwise preserved cognitive functioning. Sadly, Participant S1 also experienced the fastest disease progression of all the participants, especially in contrast with Participants S4 and S5 with nonfluent/agrammatic PPA who were able to sustain long term participation in treatment.

In conducting this study, we modified the design to accommodate the participants' various abilities to adhere to treatment. These modifications are best summarised in the structure of our results, presented according to whether participants completed one, two or three (or more) periods of treatment. An important clinical application of these necessary modifications relates to the fundamental goal of lexical retrieval treatment in PPA, which is to restore and maintain retrieval (and in semantic variant PPA, comprehension) of important vocabulary items for as long as possible (Croot, 2018b, Reilly, 2016), delivered within the context of person- and relational-centred care (Morhardt & Spira, 2013; Kortte & Rolaglski, 2013). Lexical retrieval treatment will only be possible when the person has access to treatment activities, and the health and motivation to carry them out, all of which may present challenges in this clinical population. Further, in the context of an inevitable downhill clinical trajectory (Robinson, 2001), individuals with PPA and their families and close others are likely to have other goals, including recreational travel or visiting family (Participants S2 and S3), that further restrict access to treatment and the opportunity to conduct daily treatment activities.

Table 13. Summary of participant factors considered in relation to immediate treatment gains and ability to continue with ongoing treatment.

	Participant							
	S1	S2	S3	M1	M2	M3	S4	S5
Gender, Age at entry	F, 57	M, 68	F, 59	M, 69	F, 64	M, 59	F, 72	F, 71
PPA variant	nfv	mixed	lv	sv	lv	sv	nfv	sv
Years post-onset	< 1	1.5	2.5	18	2	1.5	2-3	1
Information about treatment adherence								
Periods of treatment completed	One	One	One	Two, nonadherent in third period	Two, nonadherent in third period	Three	Three	Three
Reason stopped practice	Rapid decline	Travel then other adverse health event	Travel then deteriorating cognitive and mental health	Lost motivation, walking "obsessively"	Lost support in accessing treatment	End of study; wanted to continue	End of study; wanted to continue	Enrolled in new study after more than 18 months' ongoing treatment
Factors predicting ability to maintain long-term treatment								
Initial MMSE /30	26	28	25	26	20	26	25	29
Initial picture naming[1]	73	7	13	33	47	33	7	80
Initial semantic function[2]	Good	Moderately intact	Reduced	Good	Reduced	Reduced	Reduced	Good
Executive function and insight about PPA symptoms[3]	Good	Good	Reduced	Reduced	Reduced	Reduced	Reduced	Good
Episodic memory	Good	Reduced	Reduced	Reduced	Reduced	Reduced	Reduced	Good
Anxiety/ Mood disorder[4]	Nil	Mild anxiety	Anxiety	Severe depression	Mild depression	Minimal depression	Severe anxiety and depression	Nil
Spouse	Yes	Yes	No	No	No	Yes	Yes	No

KEY: nfv = non-fluent/agrammatic variant PPA, lv = logopenic variant PPA, sv = semantic variant PPA, n/a = not available. 1. percent correct

on Graded Naming Test (ref) for Participants S1, S2, S3, S4 and S5; Boston Naming Test for Participants M1, M2 and M3 . 2. Word Comprehension/Semantic Association on the Sydney Language Battery (Savage, Hsieh et al., 2013) for Participants S1, S2, S4 and S5. German version of the Repeat and Point Test based on Hodges et al. (2008) for Participant M1, German version of the Repeat and Point Test and the BOSU (Glindemann et al. 2002) for Participants M2 and M3. 3. Executive functioning determined on the basis of formal testing and clinical history. 4. Determined on the basis of scores on the Depression Anxiety and Stress Scale (Henry & Crawford, 2005) for Participants S1, S2, S3, S4 and S5; BDI-II (Hautzinger et al., 2006) for Participants M1, M2 and M3.

4.6 Concluding remarks

A number of intervention approaches to reduce word retrieval difficulties in PPA have been developed, utilising techniques already in use in speech pathology practice with other clinical groups (McNeil & Duffy, 2001). These range from restorative techniques that aim to reduce the retrieval impairment by reinstating knowledge of words or improving access to words, to compensatory techniques that make words, phrases or sentences available for functional use, for example by training people with PPA and their communication partners to use rehearsed scripts, communication books or boards, or text-to-speech devices. Current best practice is to select restorative and/or compensatory behavioural approaches (Kortte & Rogalski, 2013), depending on the communication needs and preferences of the person with PPA and their communication partners (Ruggero, Nickels & Croot, in prep).

The present study was conducted at two centres, the War Memorial Hospital Primary Progressive Aphasia and Related Disorders Clinic in Sydney, Australia, and the Neurology Clinic and Polyclinic at the University of Munich, Germany. This allowed for recruitment of a more diverse convenience sample of participants, and for within-study replications of the long-term treatment gains across centres, languages, and (two) PPA variants. The study supports lexical retrieval treatment as a Practice Option for semantic variant PPA and adds to the evidence for lexical retrieval treatment in nonfluent/agrammatic PPA. We have shown that Repetition and Reading in the Presence of a Picture over a long period of time can yield immediate treatment gains, and maintain them above baseline level, even, in one case, over a period approaching two years. Effects are specific to treated items, so we repeat an endorsement we have made previously to only select for treatment words that are personally and communicatively relevant for the individual with PPA. High levels of cognitive function, normal mood and support from social networks and speech pathology services were suggested as factors supporting long-term participation in treatment in our study. Not all individuals were able to persist with long-term treatment, due to disease progression, the priority of pursuing other life goals in combination with declining health, other health events, or loss of support to access treatment. Factors associated with long-term treatment adherence and gains versus nonadherence to treatment need further research to identify the candidates who are best suited to lexical retrieval treatment using Repetition and Reading in the Presence of a Picture.

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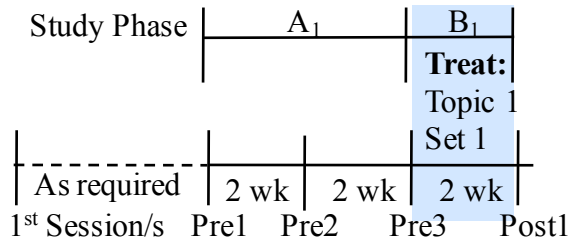
Appendix 1

Summary of treatment design carried out by each participant.

Participant S1



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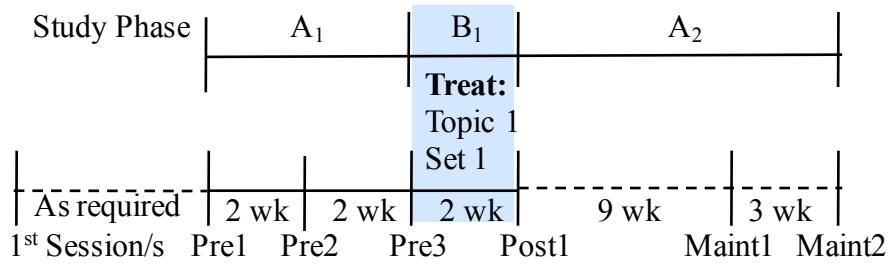
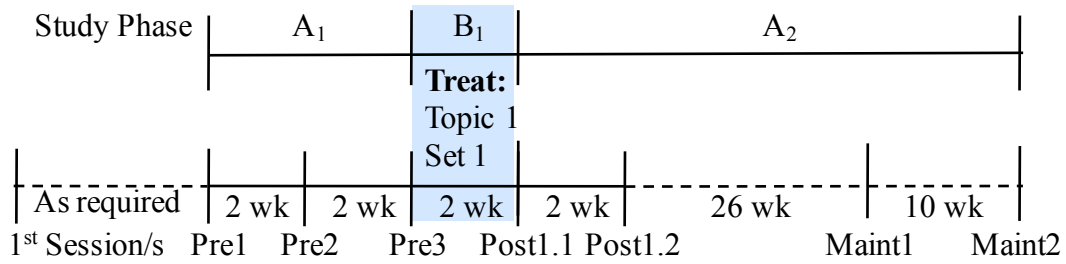
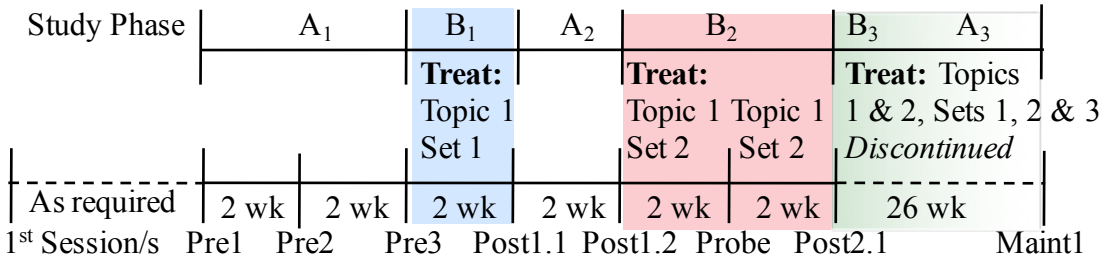


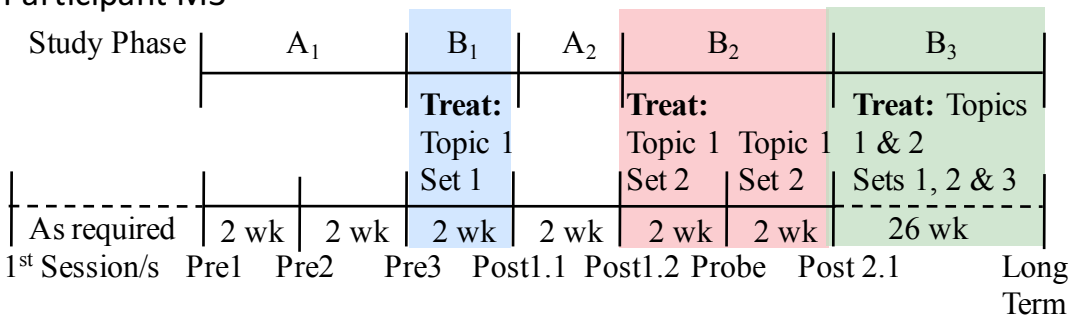
Participant S3



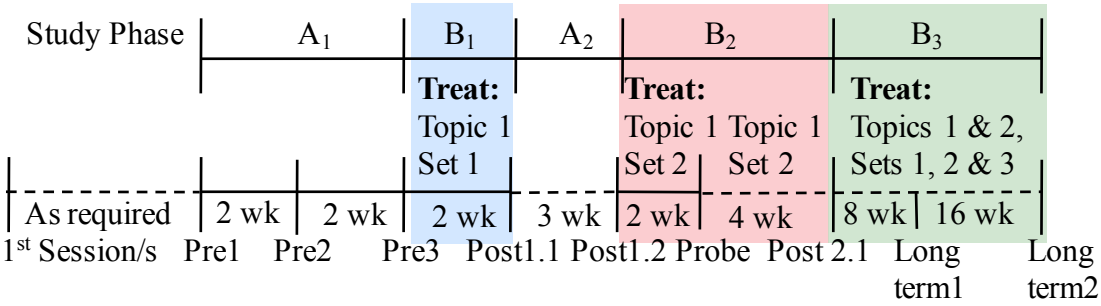
Participants M1 and M2



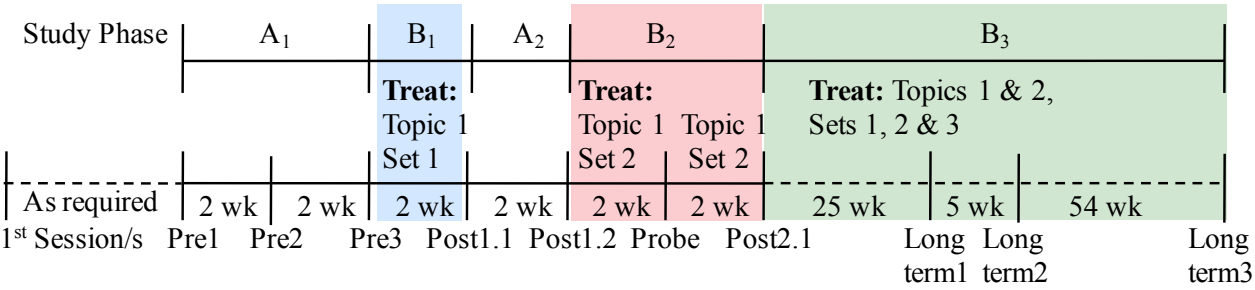
Participant M3



Participant S4



Participant S5



KEY: A_1 = Pretreatment period, B_1 = 1st treatment period, A_2 = Post-test no-treatment period, B_2 = 2nd treatment period, B_3 = 3rd treatment period. wk = week, Pre 1 = 1st Pretreatment session, Pre 2 = 2nd Pretreatment session, Pre 3 = 3rd Pretreatment session, Post 1.1 = 1st session following 1st treatment period, Post 1.2 = 2nd session following 1st treatment period.

The designs can be summarised as follows. Participant S1 carried out treatment in a biphasic A_1B_1 (pre-test, treatment) design. Participants S2 and S3 carried out treatment in a pre-test post-test design with $A_1B_1A_2$ periods. Participants M1 and M2 carried out treatment following a pre-test-post-test component in periods $A_1B_1A_2$ and an additional treatment period B_2 where treatment duration was twice as long as in the first treatment period. Because these participants discontinued treatment during Period B_3 (although it is not clear exactly when), Period B_3 is treated as incomplete and participants are presumed to have

completed their final assessment after a no-treatment period of indeterminate duration. Their design can be summarised as $A_1B_1A_2\ B_2(B_3)\ A_3$. Participant M3 followed the intended $A_1B_1A_2\ B_2B_3$ design, carrying out long-term practice after the treatment duration manipulation within the design, as did participants S4 and S5. Minor changes to the timing of assessments for S4 resulted in 6 rather than 4 weeks' treatment during period B_2, and Participant S5 completed 58 weeks' additional long-term practice.

Appendix 2

Semantic categories of treatment items selected by participants and their family members in discussion with a speech pathologist.

Participant	Categories in Sets 1 and 2 (n Items Set 1, Set 2, Total)	Categories in Set 3 (n Items Total)
S1	Important people, places, interests, transport, weather (32, 32, 64)	Food, meals, kitchen items, personal items, appliances, furniture (64)
S2	Work, finance, travel, animals (29, 29, 58)	Food, meals, kitchen items, household items, rooms, home maintenance (59)
S3	Places, park, café, garden, technology (28, 28, 56)	Important people, appointments, cooking, home items, Judaism (56)
S4	Local places, travel destinations, transport, occupations (32, 31, 63)	Sports and activities, foods, entertainment, gardening (63)
S5	Gardening, crafts, cooking, local places, computer (30, 30, 60)	Important people, family activities, numbers, appointments (58)
M1	Politicians, geography, weather, animals, interests (32, 32, 64)	Places, groceries, sport, household objects, festivals, appointments (60)
M2	Food, household activities, seasons, doctors and symptoms (32, 32, 64)	Clothes, jewellery, household items, rooms, interests, professions (63)
M3	Travel, family, tools, objects, animals (60)	Fruit, vegetables, groceries, interests, personal items (62)

Appendix 3

Description of the statistical analyses conducted to investigate immediate treatment-related gains and maintenance of gains with and without ongoing treatment using WEighted STatistics (Howard, Best & Nickels, 2015).

Analysis 1: Is there immediate treatment-related improvement in the first treatment period (all participants)?

We investigated immediate treatment effects and item generalisation due to the first treatment period (B_1, two weeks' duration), by examining whether for each participant:

1) over the first five sessions[4] (Pre 1, Pre 2, Pre 3, Post 1.1, Post 1.2) there was a significant trend for improvement (WEST-Trend), for each of Sets 1, 2, and 3, using a one-tailed one-sample t-test. We examined whether there were significant differences between the Trends of Set 1 versus Set 2, using a one-tailed two-sample t-test.

2) the change over treatment period B_1 was significantly different to the change over the pre-test period A_1 using weightings for evaluation of Rate Of Change (WEST-ROC), an analysis which enables evaluation of treatment effects even when there is instability during the baseline. Here we examined the Rates Of Change across the treated and the untreated periods (Pre 1, Pre 2, Pre 3, Post 1.1, Post 1.2) for each of Sets 1, 2 and 3, using a one-tailed one-sample t-test. We examined whether there was a difference in the pattern of rates of change across treated and untreated periods for the treated Set 1, versus the untreated Set 2 using a one-tailed two-sample t-test.

Analysis 2: Is naming accuracy maintained without ongoing treatment after the first period of treatment (Participants S2 and S3)?

To investigate maintenance of any gains due to the first treatment period (B_1) during the following period without treatment for Participants S2 and S3, we conducted WEST-COL analyses, which COmpare the Level of performance in two treatment study periods (Howard et al., 2015)[5]. A WEST-COL analysis that compares two test points only is equivalent to a McNemar Test. For Participants S2 and S3, we examined whether

[4] Only four sessions were analysed for Participants S1 and S2, who did not complete Post 1.2

[5] WEST-COL assumes no significant difference between sessions within a period, an assumption that was supported for all WEST-COL analyses involving more than one session per period; see Appendix 5.

1) they maintained the level of picture naming accuracy seen immediately post-treatment. WEST-COL analyses using one-tailed one-sample t-tests compared naming accuracy between the post-test session/s and the sessions following a period without treatment (Participant S2: Post 1 vs 9-week Maintenance, and vs 12-week Maintenance; Participant S3: Post 1.1 and Post 1.2 vs 26-week Maintenance and vs 36-week Maintenance). These were conducted for each set individually (Sets 1, 2, & 3) and for all sets combined, with alpha corrected to 0.05/3 = 0.017 in the first three analyses to control the family-wise error rate.

2) they maintained the level of picture naming accuracy seen at pretreatment. WEST-COL analyses using one-tailed one-sample t-tests compared naming accuracy on the pretreatment sessions (combined) with the sessions following a period without treatment (Participant S2: Pre 1, Pre 2 and Pre 3 vs 9-week Maintenance, and vs 12-week Maintenance; Participant S3: Pre 1, Pre 2 and Pre 3vs 26-week Maintenance and vs 36-week Maintenance). As above, these were conducted for each set individually (Sets 1, 2, & 3) and for all sets combined, with alpha corrected to 0.05/3 = 0.017 in the first three analyses.

Analysis 3: Is there immediate treatment-related improvement in the second treatment period (Participants M1, M2, M3, S4 and S5)?

To investigate immediate treatment effects and item generalisation due to treatment for participants who went on to complete a second period of treatment (B_2, four weeks' duration), we analysed the number of correct responses in Set 1 (now untreated), Set 2 (now treated), and Set 3 (continuing untreated) across Periods A_2 B_2 (Post 1.1, Post 1.2, Probe, Post 2.1). As in the analyses of the first treatment period, these were one-tailed one-sample t-tests conducted within each set to evaluate the trend across these time periods (WEST-Trend) and the rates of change (WEST-ROC) during untreated versus treated periods. Similarly, we conducted one-tailed two-sample t-tests to evaluate the difference in Trend and in Rate Of Change between the treated and matched untreated sets. Because Set 2 (treated) and Set 3 (untreated) both received no treatment in all five sessions preceding the second treatment period, we also conducted WEST-Trend and WEST-ROC analyses across Periods $A_1B_1A_2$ B2 (Pre 1, Pre 2, Pre 3, Post 1.1, Post 1.2, Probe, Post 2.2) with sessions Pre 1, Pre 2, Pre 3, Post 1.1 and Post 1.2 all considered as untreated in the WEST-ROC analysis.

Analysis 4: Is there an immediate effect of treatment during the first and second treatment periods combined (Participants M1, M2, M3, S4 and S5)?

To investigate whether there was an effect of treatment across the first and second treatment periods A_1B_1 A_2 B_2, we conducted WEST-Trend and WEST-ROC analyses as above on correct responses to items in Sets 1 and 2 combined (Set 1 items treated in period B_1, Set 2 items treated in period B_2), and in Set 3 (untreated), across Pre 1, Pre 2, Pre 3, Post 1.1, Post 1.2, Probe, and Post 2.2 for Participants M1, M2, M3, S4 and S5.

Analysis 5: Is there a difference in immediate treatment effect in the first versus the second treatment periods (Participants M1, M2, M3, S4 and S5)?

To determine whether the level of improvement due to four weeks' treatment of Set 2 in period B_2 was greater than due to two weeks' treatment of matched Set 1 in period B_1 we conducted a one-tailed two-sample t-test comparing WEST-COL weighted values computed over the Pre 1, Pre 2, Pre 3 and Post 1.1 sessions (pre- and post-test measures for the first treatment period B_1) against WEST-COL weighted values computed over sessions Post 1.2 and Post 2.1 sessions (pre- and post-test measures for the second treatment period B_2). Standard deviations for the weights were equalized given the unequal number of test points contributing to these two sets of weights.

Analysis 6: Is naming accuracy maintained after the first and second treatment periods following nonadherence to treatment in Period 3 (Participants M1 and M2)?

To investigate maintenance of any gains due to the first and second treatment periods over the final study period during which Participants M1 and M2 did not persist with treatment activities, we conducted two sets of WEST-COL analyses using one-tailed one-sample t-tests. Each set was conducted for each set individually (Sets 1, 2, and 3), and for all three sets combined, with alpha corrected to $0.05/3 = 0.017$ in the analyses of individual sets. For Participants S2 and S3, we examined whether

1) they maintained the level of picture naming accuracy seen immediately post-treatment. We compared Post 2.1 with the final session of the study (Participant M1: Post 2.1 vs 54-week Maintenance; Participant M2: Post 2.1 vs 35-week Maintenance).

2) they maintained the level of picture naming accuracy seen at pretreatment. We compared the Pretreatment sessions (combined) with the final session (Participant M1: Pre 1, Pre 2 and Pre 3 vs 54-week Maintenance; Participant M2: Pre 1, Pre 2 and Pre 3 vs 35-week Maintenance).

Analysis 7: Is naming accuracy maintained by long-term treatment (Participants M3, S4 and S5)?

We conducted two sets of WEST-COL analyses using one-tailed one-sample t-tests to investigate whether naming accuracy was maintained by ongoing long-term treatment of all items over the third treatment period B_3. Each set was conducted for each set individually (Sets 1, 2 and 3) and for all three sets combined, with alpha corrected to 0.05/3 = 0.017 in the analyses of individual sets. For Participants M3, S4 and S5, we examined whether

1) picture naming accuracy was better following ongoing practice relative to the end of the second treatment period. We compared naming accuracy following the second treatment period (Post 2.1) with all sessions following periods of long-term treatment (Participant M3: Post 2.1 vs 26-week Long-term practice; Participant S4: Post 2.1 vs 8-week Long-term practice, and vs 24-week Long-term practice; Participant S5: Post 2.1 vs 25-week Long-term practice, and vs 30-week Long-term practice, and vs 84-week Long-term practice).

2) picture naming accuracy was better than at pretreatment. We compared naming accuracy on the pretreatment sessions (combined) with sessions following periods of long-term naming treatment (Participant M3: Pre 1, Pre 2, Pre 3 vs 26-week Long-term practice; Participant S4: Pre 1, Pre 2, Pre 3 vs 8-week Long-term practice, and vs 24-week Long-term practice; Participant S5: Pre 1, Pre 2, Pre 3 vs 25-week Long-term practice, and vs 30-week Long-term practice, and vs 84-week Long-term practice).

Appendix 4

Weights for analyses using WEighted STatistics (WEST) for Participants S1, S2, and S3 who completed one period of treatment.

Participant S1	**Pre 1**	**Pre 2**	**Pre3**	**Post 1**			
WEST Trend	-3	-1	1	3			
WEST-ROC	2	-1	-4	3			
Participant S2	**Pre 1**	**Pre 2**	**Pre3**	**Post 1**	**9-wk Maintenance**	**12-wk Maintenance**	
WEST Trend	-3	-1	1	3	0	0	
WEST-ROC	2	-1	-4	3	0	0	
Maintenance over period without treatment (WEST-COL)							
Post vs 9-wk Maintenance	0	0	0	-1	1	0	
Post vs 12-wk Maintenance	0	0	0	-1	0	1	
Pretreatment vs 9-wk Maintenance	-1	-1	-1	0	3	0	
Pretreatment vs 12-wk Maintenance	-1	-1	-1	0	0	3	
Participant S3	**Pre 1**	**Pre 2**	**Pre3**	**Post 1.1**	**Post 1.2**	**26-wk Maintenance**	**36-wk Maintenance**
WEST Trend	-4	-2	0	2	4	0	0
WEST-ROC	2	-1	-4	3	0	0	0
Maintenance over period without treatment (WEST-COL)							
Post 1.1 Post 1.2 vs 26-wk	0	0	0	-1	-1	2	0
Post 1.1 Post 1.2 vs 36-wk	0	0	0	-1	-1	0	2
Pretreatment vs 26-wk Maintenance	-1	-1	-1	0	0	3	0
Pretreatment vs 36-wk Maintenance	-1	-1	-1	0	0	0	3

Weights for analyses for Participants M1 and M2 who completed two periods of treatment but did not adhere to treatment in the third period

Participants M1 and M2	**Pre 1**	**Pre 2**	**Pre3**	**Post 1.1**	**Post 1.2**	**Probe**	**Post 2.1**	**54-wk Maintenance**
First treatment period								
WEST Trend	-4	-2	0	2	4	0	0	0
WEST-ROC	2	-1	-4	3	0	0	0	0
Second treatment period								
WEST Trend	0	0	0	-3	-1	1	3	0
WEST-ROC	0	0	0	3	-4	-1	2	0
Second treatment period, 5 baselines								
WEST Trend	-3	-2	-1	0	1	2	3	0
WEST-ROC	3	1	-1	-3	-5	0	5	0
First and second treatment periods combined								
WEST Trend	-6	-4	-2	0	2	4	6	0
WEST-ROC	1	0	-1	0	-1	0	1	0
Second vs first treatment period (WEST COL)								
First treatment period	-1	-1	-1	3	0	0	0	0
Second treatment period	0	0	0	0	-1.414214	0	1.414214	0
Maintenance over period without treatment (WEST-COL)								
Post 2 vs Maintenance[1]	0	0	0	0	0	0	-1	1
Pretreatment vs Maintenance[1]	-1	-1	-1	0	0	0	0	3

1. Maintenance over a period of non-adherence to treatment for Participant M1 was 54 weeks, and for Participant M2 was 35 weeks.

Weights for analyses for Participants M3, S4 and S5 who completed three periods of treatment. 1. Different intervals between sessions for these participants account for differences in weights

Participant M3	**Pre 1**	**Pre 2**	**Pre3**	**Post 1.1**	**Post 1.2**	**Probe**	**Post 2.1**	**26-wk long-term**		
As for Participants M1 and M2, except final set of WEST-COLs for Participant M3 compare Post 2.1 with a final session following long-term treatment, not a maintenance session after a period of nonadherence to treatment.										
Participant S4	**Pre 1**	**Pre 2**	**Pre3**	**Post 1.1**	**Post 1.2**	**Probe**	**Post 2.1**	**8-wk long-term**	**24-wk long-term**	
First treatment period										
WEST Trend	-21	-11	-1	9	24	0	0	0	0	
WEST-ROC	41	-25	-91	87	-12	0	0	0	0	
Second treatment period										
WEST Trend	0	0	0	-17	-5	3	19	0	0	
WEST-ROC	0	0	0	28	-32	-15	19	0	0	
Second treatment period, 5 baselines										
WEST Trend	-47	-33	-19	-5	16	30	58	0	0	
WEST-ROC	175	73	-29	-131	-284	-93	289	0	0	
First and second treatment periods combined										
WEST Trend	-47	-33	-19	-5	16	30	58	0	0	
WEST-ROC	695	89	-517	49	-860	-294	838	0	0	
Second vs first treatment period (WEST COL)										
First treatment period	-1	-1	-1	3	0	0	0	0	0	
Second treatment period	0	0	0	0	-1.414214	0	1.414214	0	0	

Maintenance over period with ongoing treatment (WEST-COL)										
Post 2 vs 8-wk long-term	0	0	0	0	0	0	-1	1	0	
Post 2 vs 24-wk long-term	0	0	0	0	0	0	-1	0	1	
Pretreatment vs 8-wk long-term	-1	-1	-1	0	0	0	0	3	0	
Pretreatment vs 24-wk long-term	-1	-1	-1	0	0	0	0	0	3	
Participant S5	**Pre 1**	**Pre 2**	**Pre3**	**Post 1.1**	**Post 1.2**	**Probe**	**Post 2.1**	**25-wk long-term**	**30-wk long-term**	**84-wk long-**
As for Participant M3, but there are three sessions assessing lexical retrieval over an ongoing period of long-term treatment for Participant S5.										

Weights for tests of WEST-COL assumption of no increase over the first period in the analysis for all participants (except Participant S1 for whom no WEST-COL analyses were conducted).

Participant S1	**Pre 1**	**Pre 2**	**Pre3**	**Post 1.1**	**Post 1.2**
WEST-COL Pre 1 vs Pre 2	-1	1	0	0	0
WEST-COL Pre 1 vs Pre 3	-1	0	1	0	0
WEST-COL Pre 2 vs Pre 3	0	-1	1	0	0
WEST-COL Post 2.1 vs Post 2.2	0	0	0	-1	1

Appendix 5

Test of Assumptions of level baseline for WEST-COL Analyses

	Set 1			Set 2			Set 3			All Items		
Sessions compared	**t**	**df**	**p**	**t**	**df**	**p**	**t**	**df**	**p**	**t**	**df**	**P**
Participant S2												
Pre 1 vs Pre 2	-0.37	28	0.644	-1.80	28	0.959	0.63	58	0.266	-0.45	116	0.672
Pre 1 vs Pre 3/ WEST-Trend	0	28	0.500	-1.14	28	0.868	-0.28	58	0.608	-0.78	116	0.782
Pre 2 vs Pre 3	0.33	28	0.373	0	28	0.500	-0.83	58	0.795	-0.38	116	0.646
Participant S3												
Pre 1 vs Pre 2	-1.00	27	0.837	-0.81	27	0.788	-1.76	55	0.958	-2.17	111	0.996
Pre 1 vs Pre 3/ WEST-Trend	-2.42	27	0.989	-1.44	27	0.920	-0.90	55	0.815	-2.51	111	0.993
Pre 2 vs Pre 3	-1.36	27	0.908	-0.81	27	0.788	0.83	55	0.205	-0.41	111	0.658
Post 1.1 vs Post 1.2	-0.30	27	0.616	-0.44	27	0.669	-0.83	55	0.795	-0.93	111	0.822
Participant M1												
Pre 1 vs Pre 2	-1.00	31	0.838	-2.68	31	0.994	-1.16	59	0.874	-2.09	123	0.981
Pre 1 vs Pre 3/ WEST-Trend	-0.37	31	0.644	-2.88	31	0.996	-1.07	59	0.856	-0.82	123	0.792
Pre 2 vs Pre 3	0.57	31	0.286	-1.79	31	0.959	0	59	0.500	1.39	123	0.083†
Participant M2												
Pre 1 vs Pre 2	0.37	31	0.356	0	31	0.500	0.30	62	0.383	0.41	126	0.342
Pre 1 vs Pre 3/ WEST-Trend	0.44	31	0.331	-0.70	31	0.756	0.90	62	0.185	0.41	126	0.342
Pre 2 vs Pre 3	0	31	0.500	-0.63	31	0.732	0.70	62	0.242	0	126	0.500

Participant M3												
Pre 1 vs Pre 2	n/aº	29	ns	-1.00	29	0.837	0	56	0.500	-0.33	116	0.630
Pre 1 vs Pre 3/ WEST-Trend	n/aº	29	ns	-1.00	29	0.837	0.70	56	0.242	0.33	116	0.370
Pre 2 vs Pre 3	n/aº	29	ns	0.00	29	0.500	1.43	56	0.080†	1	116	0.160
Participant S4												
Pre 1 vs Pre 2	1	31	0.163	1.36	30	0.092†	1.76	62	0.042*	2.40	125	0.009*
Pre 1 vs Pre 3/WEST-Trend	-0.44	31	0.669	0.44	30	0.331	1	62	0.161	0.69	125	0.247
Pre 2 vs Pre 3	-1	31	0.838	-1	30	0.837	-0.90	62	0.815	-1.62	125	0.946
Participant S5												
Pre 1 vs Pre 2	1	29	0.163	1.65	29	0.055†	4.06	57	<0.001*	3.879	117	<0.001*
Pre 1 vs Pre 3/WEST-Trend	0	29	0.500	0.53	29	0.301	2.21	57	0.016*	1.680	117	0.048*
Pre 2 vs Pre 3	-1.14	29	0.868	-1.16	29	0.873	-1.69	57	0.952	-2.31	117	0.989

KEY: All one-tailed p-values are right-tailed, to evaluate the null hypothesis of no increase from the earlier to the later pretreatment session. Grey shaded cells indicate significant and marginally significant results. * = significant at $\alpha = 0.05$, † = marginally significant at $\alpha = 0.01$ n/aº = unable to calculate t because scores identical on all 3 pretest sessions, indicating no difference between pretreatment sessions.

WEST = Weighted Statistics, COL = Change of Level. Note that the WEST-COL analysis comparing Pre 1 versus Pre 3 is the same as a WEST-Trend analysis over the three pretest sessions to test the null hypothesis of no significant positive trend over the three pretreatment sessions.

Chapter 3

Measuring gains in connected speech following treatment for word retrieval: A study with two participants with primary progressive aphasia

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Measuring gains in connected speech following treatment for word retrieval: A study with two participants with primary progressive aphasia

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Running head: Measuring connected speech in PPA

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Abstract

Background: The aim of lexical retrieval treatment for people with anomia is not just to improve accessibility of lexical items for confrontation naming, but to carry over this improvement to communicative situations. However, there is no consensus on what measures are the most suitable to evaluate whether such changes have occurred. Anomia is one of the core presenting symptoms for people with primary progressive aphasia (PPA), yet while there is increasing evidence for the efficacy of word retrieval treatments in PPA, there is minimal information about how improvements in picture naming transfer to connected speech.

Aims: This paper evaluates a word retrieval treatment targeting personally relevant words conducted with two people with PPA, focussing on patterns of generalisation.

Methods and Procedures: The study is a single-blind single case experimental design conducted with 2 individuals with PPA. Participants and primary communication partners identified words related to 2 topics that are personally relevant for conversation. Participants completed 3 baseline and 1 or 2 post-test measures of their ability to produce these words in picture naming and a structured interview. Therapy activities lasting 10-15 mins/day were carried out over a 2-week period at home, with participants viewing a picture of each target word on a computer screen together with its written and spoken name, and repeating/reading the name. Half the words from one topic were treated; a matched set of words from the treated topic as well as words from the untreated topic served as controls to allow us to assess generalisation within and across topic.

Outcomes and Results: At post-test, the participants' naming improved for the treated items, showing generalisation to different pictures of these items. There was neither generalisation to untreated items, nor to retrieval of the same words in a structured interview.

Conclusions: Further research is required to understand the limits and the potential of word retrieval treatments to improve conversation in both acute-onset and progressive aphasia.

Keywords: connected speech; conversation; generalisation; progressive aphasia; frontotemporal dementia; Alzheimer's disease

Measuring gains in connected speech following treatment for word retrieval: A study with two participants with primary progressive aphasia

It is now well established that treatment for word retrieval impairments in acute-onset aphasia usually results in improvements in confrontation naming, and that often these improvements are restricted to treated items (e.g., Nickels, 2002; Wisenburn & Mahoney, 2009; for an investigation of factors affecting generalisation to untreated items see Best, Greenwood, Grassly, Herbert, Hickin, & Howard, 2013). Given these findings, it is clear it is important to choose items for treatment that are functionally relevant for the individual. How to decide which items those are is far from straightforward (Renvall, Nickels & Davidson, 2013a). This is particularly in view of the fact that, while most of the treatment has concentrated on nouns, and, to a lesser extent, verbs, a large proportion of the words used most frequently in our daily communication are from other word classes such as adjectives, adverbs and pronouns (Renvall et al., 2013a). Moreover, there is little evidence about the extent to which these other word classes are amenable to treatment. While Renvall, Nickels and Davidson (2013b) provide some pointers towards how we might select functionally relevant items for treatment, this remains a difficult task.

These are not the only challenges. Treatment also aims to carry over improvement in confrontation naming to use the of these items in communicative situations. However, there is no consensus on how to evaluate whether such changes have occurred. This paper presents a study in which personally relevant topics were selected collaboratively by the participants, their partners, and the speech-language pathologist for treatment. We discuss the challenges involved in both choosing items that will be useful in daily communication and in measuring the extent to which any improvement in lexical retrieval in naming transfers into communication more broadly.

We illustrate these challenges using two single case studies of treatment for lexical retrieval impairments in people with primary progressive aphasia (PPA). A wide range of language treatments that are effective for acute-onset aphasia produce reliable gains on treated items in people with PPA (Croot et al., 2009). In the PPA literature, as in the acute-onset aphasia literature, there is minimal evidence for generalisation to untreated items or to other language tasks. Some results do suggest generalisation may occur in PPA (Beeson, King, Bonakdarpour, Henry, Cho, & Rapcsak. 2011; Henry, Beeson, & Rapcsak, 2008, Newhart, Davis, Kannan, Heidler-Gary, Cloutman, & Hillis, 2009; Savage, Piguet, & Hodges, 2014). Such results need replication, and the scope of any generalisation

(across participants, materials, and/or tasks) in PPA awaits systematic investigation.

Picture naming and conversation

Herbert, Hickin, Howard, Osborne, and Best (2008) found that accuracy of word retrieval in picture naming directly related to success in content word retrieval in conversation (Herbert et al. 2008). As they note, the fact that lexical retrieval in picture naming is quantitatively similar to lexical retrieval in conversation is predictable given that the same mental processes are involved: lexical semantic activation and processing, access to phonological forms, and articulatory representations. It follows that if retrieval of a lexical item is improved in picture naming then that lexical item will also be more accessible when its retrieval is required in conversation. Of course, there are additional conceptualisation, formulation and articulatory demands in conversation that are absent in picture naming, such that successful retrieval in picture naming may not be sufficient to predict retrieval in conversation.

In addition, it is possible that what has been learned or facilitated in treatment is not the mapping between a concept and a particular lexical item, but the mapping between a particular picture and a lexical item. Many, if not most, studies treat the same pictures that they use to measure the benefit from that treatment. There is a danger that it is not lexical retrieval that has improved, but the participant's knowledge of which precise name we want them to produce for that particular picture, or their learning of an association between a specific visual image and a phonological form. It is clear that this is not always the case, however. For example, in their seminal study, Howard, Patterson, Franklin, Orchard-Lisle and Morton (1985) used different exemplar pictures in the therapy and assessment phases and found clear improvements. Nevertheless, there are studies which have found a difference in performance between pictures used in treatment and different exemplars of the same targets. For example, Snowden and Neary (2002) found that in a case of semantic dementia even a change in the background colour of the picture gave a reduction in accuracy. Consequently, in any evaluation of whether improved word retrieval in naming generalises to communicative contexts, we must first demonstrate that it is the word retrieval processes that have improved. In the study reported below, we use different exemplar pictures for the target in the treatment phase to those used in the assessment phase.

Measurement of transfer from naming to communication

The question of how to best measure transfer from picture naming to everyday communication is non-trivial. It is generally agreed that improved word retrieval in conversation is desirable. Nevertheless, that may not mean that conversation is the best or fairest measure of transfer, nor that this level of generalisation is a reasonable goal for some individuals. We return to this below, but first discuss evidence for generalisation from word retrieval treatments to conversation and connected speech.

Carragher, Conroy, Sage and Wilkinson (2012) reviewed the five studies in the literature which, at that point, had investigated transfer from impairment-focused lexical treatment into conversation in acute-onset aphasia. The results of these studies were mixed and far from straightforward. For example, one study reported increased production of nouns per turn for one participant, but not the other (Hickin, Herbert, Best, Howard, & Osborne, 2007) and another study even found *reduced* lexical diversity following treatment (Boo & Rose, 2011). In a larger study, Best, Grassly, Greenwood, Herbert, Hickin, and Howard (2011) examined change in conversation in 13 people with aphasia who had participated in a treatment for naming (11 of whom had shown significant improvement in naming). Overall, the group showed no significant changes in any of the conversational measures they included: minimal turns as a proportion of total turns, word errors per content word, word errors per turn, content words per substantive turn, nouns per substantive turn, nouns per 5 minutes of conversation. When the data were analysed as a case series (for discussion of group vs case series design see e.g. Nickels, Howard, & Best, 2011; Schwartz & Dell, 2010), however, significant changes were seen in around a third of individuals, but not always in the predicted directions. For example, two people with aphasia showed a reduction in minimal turns (turns in which the floor is simply handed back to the conversational partner) - indicating more 'content' to their turns. One of these people, also showed an increase in word errors whereas a decrease would have been predicted. Overall, there was a significant relationship across the case series between the amount of change in naming following treatment, and the change in number of nouns per 5 minutes of conversation and the number of nouns per substantive turn. Conclusions about transfer from naming treatment to conversation therefore depend on the participants considered, the conversational measure, and the analysis (group versus case series).

In general, those studies that report generalisation to improved lexical retrieval in conversation (e.g., increased content word production or decreased content word errors) seem to be those where the individual also showed generalisation to untreated items in naming (e.g. Greenwood, Grassly, Hickin, & Best, 2010; Hickin et al., 2007 (Participant

HM)). In contrast, those studies with item-specific improvements often failed to show improvement in conversational measures (e.g. Herbert, Gregory & Best, 2014 (lexical treatment); Hickin et al., 2007 (Participant PH)). This makes sense – if item-specific effects are found in treatment and those items are not those required in the particular conversation sampled, then no change would be expected in conversation. This is one of the major problems in measuring transfer from naming to conversation.

While the ecological validity of sampling natural conversation is clear, the methodological problems that ensue are considerable. As noted, there is the problem of whether the experimental stimuli are appropriate lexical targets in a conversation sample, and appropriateness will vary from sample to sample with changes in the topic of conversation. In addition, there are problems of obtaining stable measures. Best et al. (2011) note that there were several individuals where the variability across pre-treatment baseline conversations measures was large and hence patterns following treatment were impossible to interpret. This seems to be a problem inherent to conversation. Differences in conversational topic from one sample to another can lead to different degrees of success in lexical retrieval (with differing vocabulary requirements). They may also lead to different roles for each speaker in the conversation depending on, for example, who takes the lead in a topic (e.g. discussions on planning a joint activity vs a recount of one partner's activity). In turn this may impact on the number and type of a speaker's turns.

What alternatives might there be to sampling natural conversation? Some studies have attempted to increase both pre-treatment baseline stability, and participants' opportunities to produce the experimental stimuli by using more controlled connected speech tasks, including description of composite pictures or videos containing experimental stimuli (e.g. Conroy, Sage, & Lambon Ralph, 2009; Savage, Piguet, & Hodges, 2014). However, the demands of these tasks remain very different to those of conversation with, amongst other things, lower demands on 'thinking for speaking' because of the more constrained topics and increased (implicit) guidance on narrative focus (Dipper, Black & Bryan, 2005; Marshall, 2009; Nickels, Byng, & Black, 1991). Conroy et al. (2009) found significant differences between retrieval of target words in picture description (Cookie Theft) and narrative (Cinderella), even though both tasks showed improvements and a correlation with accuracy of target naming in picture naming. Moreover, in response to pictures or videos some people with aphasia will tend to display "hypernaming", naming individual items within the event rather than describing the event itself, and may use reduced grammatical structure (e.g. Byng, Nickels, & Black, 1994;

Cairns, Marshall, Cairns, & Dipper, 2007). This suggests that these tasks are also less than optimal for investigating generalisation to connected speech.

Other researchers have attempted to maintain some ecological validity by using connected speech in a conversational setting, where they impose structure on that conversation by directing the topic so that experimental items are required. For example, Mason, Nickels, McDonald, Moses, Makin, and Taylor (2011) treated personally relevant stimuli which were divided into topics. They used a semi-structured conversation as an outcome measure. In order to increase the likelihood of a target word being produced, the clinician began the conversation by asking a question related to one of the particpant's topics. For example, for one participant, some targets related to pottery, and so conversation began with a question about her latest pottery project. Using this method, Mason et al. demonstrated that, for at least one of their two participants who showed improved naming, treated words were also produced in the structured conversations. However, these semi-structured conversations often felt far from natural. Specific questions were often required in the quest to elicit experimental items. Other authors seem to have encountered similar issues. Savage et al. (2014) note that in their video description task they used prompts such as "What is this called?" to ensure all elements of the video were addressed. These semi-structured conversations were still not immune from problems of baseline stability.

In the study presented here, we chose to use a similar technique to that of Mason et al. - a structured interview. In an attempt to increase baseline stability we put more emphasis on the talk of the person with aphasia (hence the title 'interview' rather than conversation) with the interviewer using a small number of standard questions around set topics. These topics also guided the choice of stimuli for each participant. The stimuli chosen were those potentially needed when responding to the questions in the interview. The participants in our study were individuals with PPA, so that we could begin to address the open questions about whether gains in naming would transfer to untreated items and to a structured interview in this clinical group. We will therefore now briefly outline the relevant features of, and literature on, PPA.

Primary progressive aphasia and the treatment of word retrieval

Primary progressive aphasia (PPA) is a clinical syndrome associated with frontotemporal lobar degeneration pathology or Alzheimer-type pathology in language areas of the brain (Gorno Tempini et al., 2011). There are three clinical variants of PPA

recognized in the recent consensus paper (Gorno Tempini et al., 2011): nonfluent/agrammatic, semantic and logopenic. The nonfluent/agrammatic variant (nfvPPA) is characterized by agrammatic language production and/or apraxia of speech, the semantic variant (svPPA) by impaired confrontation naming and single word comprehension, and the logopenic variant (lvPPA) by anomia and impaired repetition of sentences and phrases. Difficulties in word retrieval are an early, prominent and debilitating symptom for people with all three variants of PPA (Mesulam, 2001). PPA has a profound effect on a person's ability to communicate, which in turn affects a person's relationships, social networks and ability to participate in a multitude of everyday activities that depend on communication (Nickels & Croot, 2014).

There is a limited number of published research findings on appropriate interventions for primary progressive aphasia, but there is evidence that language treatments effective with acute-onset aphasia are also effective for people with progressive aphasia (Croot, Taylor, & Nickels, 2011; Nickels & Croot, 2009). A range of lexical retrieval interventions result in better performance for retrieval of treated items compared to pre-treatment baseline and/or untreated items immediately post-treatment in PPA (see Jokel, Graham, Rochon, & Leonard, 2014 for a review). Generalisation to untreated items is rare, but sometimes may be possible to some untrained items and categories (Henry et al., 2008, Newhart et al., 2009; Beeson et al., 2011). Although generalisation of treatment effects to everyday communication is difficult to measure, there are reports by people with PPA and their family members of treated items and functional communication improving outside the clinic concurrent with gains measured on treated tasks and items (e.g. Beeson et al., 2011; Heredia, Sage, Lambon-Ralph, & Berthier, 2009; Jokel & Anderson, 2012)

Given that speech pathology provision to people with PPA is often limited (e.g. Taylor, Kingma, Croot, & Nickels, 2009), further research into the efficacy and effectiveness of treatments for PPA is important. The present study aimed to evaluate a word retrieval treatment targeting personally-relevant words in PPA, with a specific focus on patterns of generalisation. We used a standard treatment for word retrieval disorders used in acute-onset aphasia (Repetition and/or Reading In the Presence of a Picture; RRIPP). We have collected data from a case series of 10 participants, but as the study is still in progress, we focus here on the results from the first two participants. We investigated whether a) treatment with RRIPP was effective with personally-relevant words in personally-chosen topics; b) the treatment gains reflected improvements in word retrieval rather than learned mappings between a trained image with a lexical item (using

different exemplars of the target stimuli during treatment and assessment phases); c) the lexical retrieval gains in picture naming generalised to connected speech in a structured interview.

Method

Participants

Participants were two people with PPA, CSN and DQI, diagnosed using the consensus criteria (Gorno-Tempini et al., 2011). Inclusion criteria were English dominant language and word retrieval deficit on screening (Graded Naming Test, McKenna & Warrington, 1997). Exclusion criteria were age < 40 or > 85 years, inability to give informed consent or to complete neuropsychological tasks, and contraindicated medical, psychiatric, language or central nervous system history.

CSN

CSN was an 80 year old male former senior civil servant, with a 4 year history of speech and language deterioration when he entered this study. MRI one year earlier showed frontal and left perisylvian atrophy. CSN was diagnosed with nfvPPA associated with corticobasal syndrome, apraxia of speech, motor apraxia involving right hand, and extrapyramidal motor signs. His language was effortful, with halting speech and impaired word retrieval. Comprehension and repetition were good, but spontaneous speech was described as poor in the neurologist's initial clinical evaluation. His score of 18/30 on the Graded Naming Test was just above the 25th percentile for controls (Warrington, 2010). On the Comprehensive Aphasia Test (Swinburn, Porter, & Howard, 2005), CSN also scored within normal limits on tests of spoken and written word and sentence comprehension, spoken paragraph comprehension, naming objects and actions, word and nonword repetition and reading and sentence repetition.

DQI

DQI, was a 54 year old female former secretary. She had a 5 year history of speech and language deterioration at the start of the study. MRI one year earlier noted dilatation of the left lateral ventricle and mild parietal atrophy, particularly on the left. DQI was diagnosed with lvPPA. She had fluent, grammatical, well articulated expressive language with impaired word retrieval. Comprehension and word repetition were good, but spontaneous speech output and sentence repetition were poor. She scored 5/30 on the

Graded Naming Test, below the 1st percentile (Warrington, 2010). On the Comprehensive Aphasia Test (Swinburn et al., 2005), DQI scored within normal limits on written sentence comprehension, spoken paragraph comprehension, and naming of objects and actions.[1] She could repeat sentences with four but not five content words.

Materials and Procedure

Stimuli were individually chosen words or phrases related to two personally relevant topics (Topics 1 and 2; approximately 60 words per topic). Topics and stimuli were generated through informal conversation with participant and their spouse during the first week of the study (Figure 1). For CSN one topic centred around family and personal history narrative (education, work) and the other around current hobbies and activities. For DQI, one topic centred around daily activities at home, and the other on social activities and interests outside the home. For example, DQI took a daily walk along the beach, thus stimuli were collaboratively chosen to include things she may have wished to discuss such as "jellyfish", "low tide" and “pink sunset”. In selecting materials that were best suited to CSN’s and DQI’s interests, there was no attempt to match materials across participants, nor to match items across treated and untreated topics within participant, apart from attempting to find items for both topics that were important to the participants. Treated versus untreated items within the treated topic for each participant were, however, matched as closely as possible (see below and Appendix 1).

To ensure generalisation of word retrieval beyond association with a specific picture, for each stimulus item, two different pictures were selected, one was used at pre-treatment baseline and post-test, and one during treatment,. For items that were not easily or uniquely depictable, the picture was paired with a definition or sentence cue. For example, the picture for “low tide” (showing water far down a beach) was paired with the description "The water is really far out", and for “nonfiction,” a picture of a history book was paired with "Writing based on facts or historical events".

[1] Comprehensive Aphasia Test naming items are much higher frequency than items in the Graded Naming Test

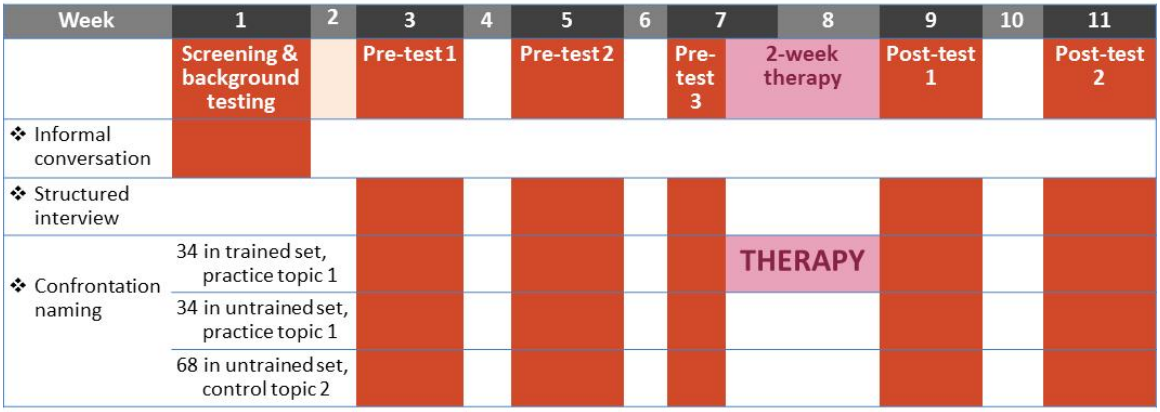

Figure 1. Timeline for the study

Each item was presented for naming on three separate occasions prior to treatment, and twice after treatment for CSN; once for DQI for reasons explained below. The timeline for the larger study, followed by CSN, is shown in Figure 1. CSN also completed a follow-up session 1 month after the second post-test without further treatment. This was intended as a probe for monitoring maintenance after six months of home treatment on all items, however he was unable to maintain the home practice for that long, as noted in the Discussion. DQI lived several hundred kilometres from the study centre and was only able to attend when visiting Sydney, so her three pre-treatment baseline assessments were conducted on the Monday, Wednesday and Friday of a single week. The speech pathologist who conducted the baseline structured interviews conducted DQI's post-test interview by Skype, and a local speech pathologist conducted the post-test naming test using the study materials according to the study protocol. Naming responses were transcribed from video and scored following standard procedures. DQI was unavailable for a second post-test session shortly after treatment because she was on vacation. She completed a 9-month follow-up session on her next visit to Sydney.

In each of the picture naming assessments, items from the different topics were presented intermixed and in the same random order on each assessment on a computer monitor. Participants were given 5 seconds to name the picture before it was removed from view. Progress to subsequent items was self-paced. Naming responses were transcribed on-line by the clinician administering the assessment and video-recorded for subsequent verification of the on-line transcription and coding by coders who were blind to the treatment condition of the items. The final response within 5 seconds was coded as correct, as an acceptable alternative (another name that would be acceptable for the picture but not the original target), semantically-related response, semantic description, phonologically-

related response, mixed (semantic and phonologically related) response, unrelated response, no specific response (includes no response and nonspecific comments such as "Oh its one of those things") or other response (e.g. naming a part of the picture; visually-related response). In his first pre-therapy assessment CSN scored 30% correct (32% including acceptable alternatives). The majority of his non-target responses were no specific response (43% of responses) with occasional semantic descriptions (2%). DQI scored 48% correct in her first pre-therapy assessment (52% including self-corrections and acceptable alternatives). The majority of DQI's non-target responses were semantically-related (21% of responses, including superordinates "yoga" → "exercise", category co-ordinates "body-boarder" → "surfer", and subordinates "casserole" → "chicken") and no specific response (13% of responses)[2].

For each participant, one of the two topics was randomly allocated to the treatment condition, and words within the treated topic were randomly allocated to treated and untreated sets. These sets were matched for accuracy and number of errors of each type made during pre-treatment Baseline 1 and Baseline 2, and for the number of words that appeared in the structured interviews on these baselines. Baseline 3 was conducted immediately prior to the therapy materials being provided thus could not be included in the matching. In addition, sets were matched for log spoken word frequency from CELEX (Baayen, Piepenbrock, & van Rijn, 1993) and log total word frequency, number of words in the target, number of syllables, number of phonemes, number of letters, number of words in each sub-category within the topic (e.g. 8 objects, 7 book-related words and 2 names of family members per set for CSN), and number of items presented with a definition/cue. See Appendix 1 for stimuli and details of stimulus matching across treated and untreated sets for both CSN and DQI.

In addition to naming, we investigated word retrieval in a structured interview on the chosen topics. The interview was conducted by the same speech pathologist, shortly after the naming assessments, at each time point: three times before and twice after treatment (CSN) and once after treatment (DQI) with a 1-month follow-up (CSN) and a 9-month follow-up (DQI). The interview was structured in the sense that the speech pathologist asked similar questions on each occasion to elicit conversation about the

[2] Overall percentage correct for each participant reflects their anomia relative to the items selected as personally relevant for them. Different items for each participant mean that success is not directly comparable across individuals.

treated and untreated topics, and attempted to minimise other input into the conversation (see Tables 1 and 3 for examples of interview questions).

The structured interviews were audio- and video-recorded, and transcribed from the audio recording with transcriptions checked against the video recording by a second researcher. We counted total words, i.e., the sum of words occurring in the following categories: target words (the experimental stimuli in the trained and untrained topics), other content words, closed-class words, fillers (e.g. "um", "er", and the words "yes" and "no," as a measure of each participant's contributions to conversation. Numbers (referring to dates e.g. "forty-six" and ages, e.g. "six" were included in the "other content words" category). Because the participants' use of target words was at near-floor level, we used lenient criteria to count target words in the interview (e.g. we accepted a commonly used shortened form of the name of CSN's school), but this only increased the counts for two target words. The ratio of content words (target words plus other content words) to total words (minus fillers and yes/no responses) was calculated as a measure of information content in the participants' interview responses.

The speech pathologist who performed the pre-treatment baseline and post therapy assessment was blind to the allocation of topics and targets to treatment. The treatment task was therefore developed and introduced to the client by a second speech pathologist.

Treatment:

Items in the treatment set (N = approximately 30 for each participant) were treated using Repetition and/or Reading in the Presence of the Picture (RRIPP), presented using Powerpoint. The second pictorial exemplars of the stimuli (i.e., different pictures to those used at pre-treatment baseline and post-test) were presented one at a time, for 5 seconds, on a computer screen. Simultaneously with picture presentation, the written name was presented below the picture and a sound file played the spoken name of the item. Participants were required to say the name of the picture, using the auditory and written form to assist them in reading/repeating the target. When the word and picture disappeared after 5 seconds, participants saw a screen with a central asterisk, and could advance to the next item by pressing the space bar. Five versions of the file were prepared (one for each day of treatment in the week), with the stimuli presented in different random orders, to prevent the potential for rote learning if materials were always practised in the same order (Graham, Patterson, Pratt, & Hodges, 1999). Item order in the treatment files also differed from the order in the pre-treatment baseline and post-test assessments. The

treatment files were installed on the CSN's own computer; DQI borrowed a study computer. In the first treatment session, participants were guided to open the file and run the presentation, monitored by the second speech pathologist. All subsequent treatment sessions were performed independently by the participant in their own home. They carried out the task once per day for 10 days over 2 weeks (5 days per week): hence each target item received 10 trials of therapy.

Results

Both CSN and DQI completed all 10 sessions of therapy. Effects of therapy were analysed using Weighted Statistics (Howard, Best, & Nickels, in press). First we evaluated whether over the study as a whole (taking into account data from each test point) there was a significant trend for improvement (WEST-Trend)[3]. Then we examined whether the change over the treatment period was significantly different to the change over periods with no treatment using weightings for evaluation of Rate of Change (WEST-ROC), the analysis hence controls for any instability during the baseline.

For CSN, average accuracy in naming for treated items almost doubled from pre-treatment baseline to Post-test 2 (average baseline: 37% to an average of 66% correct on the two immediate post-tests (Figure 2), but this improvement was item-specific. Across the study, from Baseline 1 to Post-test 2, there was a significant trend to improvement for the treated set ($t(33) = 4.558$, p(2-tailed) = 0.001), but not for the untreated set within the treated topic ($t(33) = -0.350$, p(2-tailed) = 0.729) nor for the untreated topic ($t(50) = 0.260$, p(2-tailed) = 0.7958). Moreover, there was a significant difference between the trends for the treated and untreated sets within the treated topic (p(2-tailed) < .001). Comparing the rate of change across treated and untreated phases, CSN showed no significant difference for the untreated set in the untreated topic ($t(51) = -0.522$, p(1-tailed) = 0.698) or in the treated topic ($t(33) = -0.8124$, p(1-tailed) = 0.788), and approached a significant effect for the treated items ($t(33) = 1.330$, p(1-tailed) = 0.096). There was a decline in his performance on the treated set over the six weeks following treatment.

[3] Note that the lack of a significant improvement over the study as a whole in cases with progressive aphasia may not mean that there has been no improvement. If the trajectory would have been downward prior to therapy then no change across the study may be a positive outcome of treatment (Rapp & Glucroft, 2009).

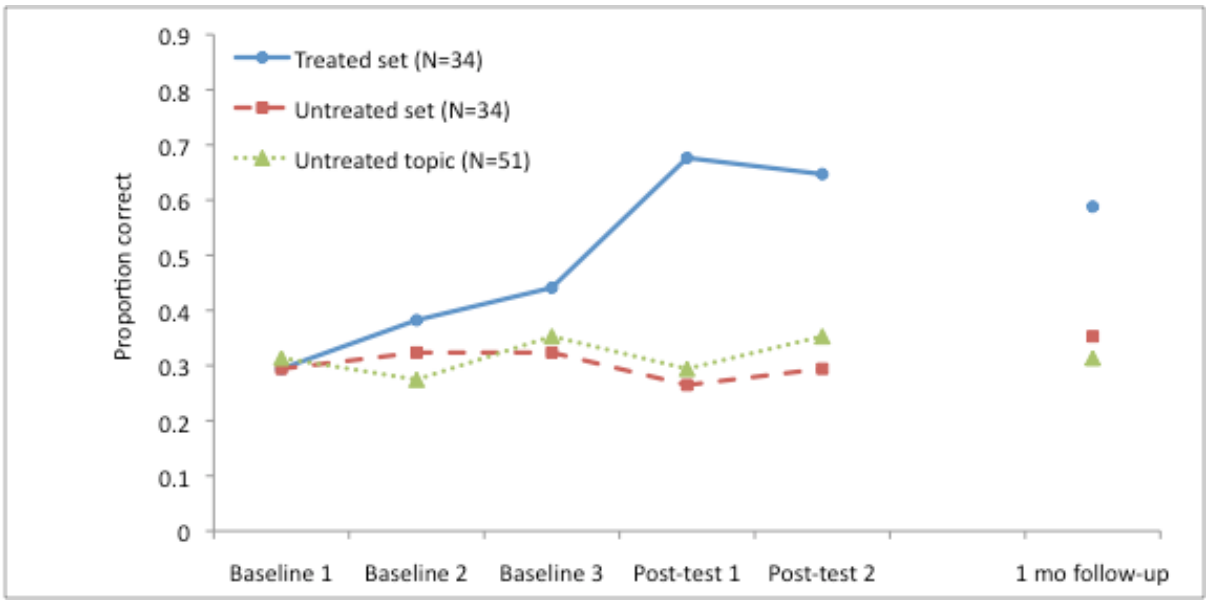

Figure 2. Proportion of pictures named correctly by CSN on each session.

CSN's improvement on picture naming was not reflected in his performance on the structured interview, where use of treated words remained at floor. Table 1 shows a sample of CSN's responses to two structured interview questions across the six sessions of the study. CSN used four different target words in the structured interviews: two words from the untreated topic appeared during the pre-treatment baseline interviews (shortened name of his school and the word "school"), he also used these after treatment. An additional two items, from the treated set, appeared for the first time after treatment (CSN's wife's name and "work"). While this may indicate a benefit of treatment (even, perhaps, a 100% gain in availability of target words in the interview), this finding is impossible to interpret as it may instead reflect sampling noise across interviews.

Table 2 summarises CSN's output in the structured interview across sessions. Total output and number of content words varied across sessions, for example, consisting of only "no" and "oh dear" on Baseline 2. CSN spoke more in response to questions about the treated compared with the untreated topic, declining to answer questions about the untreated topic altogether on Post-test 2.

CSN showed significant trend from Baseline 1 to Post-test 2 for increased production of total words, other content words (token), total content words (token) and closed class words for combined topics and for the treated topic and for total words in the untreated topic. (Poisson test for trend using lambda coefficients for rate of change

(WEST-Trend): all comparisons $z > 2.88$, and p(2-tailed) < 0.001)[4]. No conditions showed significantly greater change during the treatment phase (Poisson test for trend using lambda coefficients for rate of change (WEST-ROC): all comparisons $z < 1.79$, p(2-tailed) > 0.07; except Fillers in combined topics, $z = 2.19$, p(2-tailed) = 0.028, a value which does not survive our correction for multiple comparisons).

[4] As there were 10 analyses in each condition in the analysis of connected speech, we only consider significant values where $p < .005$.

Table 1

Samples of CSN's response to two questions within the treated topic (about early life and education) in the structured interview.

Speech pathologist	**CSN**
Baseline 1	
Tell me about your earlier life?	Oh dear. My childhood. Oh dear. No.
Or your education?	Education. I went to (colloquial name of school) in '42. Oh dear. Left there in '46. No.
Baseline 2	
Can you tell me anything about your childhood, education?	No.
Baseline 3	
Can you tell me about your childhood?	Oh…Some time ago… some time ago
Or your education?	Oh I was at (colloquial name of school) as you know. I went down there in my second year and um. I er
Can you tell me a bit more about your job?	No I no (first and surname of friend) (nodding & smiling) (laughs) Er He's in my class at school
And what about him?	(first and surname of friend) er I think uh came er ah for a um er no
He came to visit?	He came to visit and he ear er extend my year. Um attends my class at ear /r/ um
And he is in Brisbane?	No (first and surname of friend). That's OK. And I said er um ah (first and surname of friend). Um send my tend my class at school . At 82
Post-test 1	
Like in previous times. I'd like to know something about you and especially about your earlier life.	Oh. The er early life? Yes yes yes. Nought to six, I was in Queensland, er sorry was in (country town), er (country town), ah and then I (coastal town) and then (country town). Oh dear. I was nought to six and um in (coastal town) and then ere r six to eleven in Queensland er (country town).
And also something else about your education you can tell me ?	No. Er. Dear. Er. Um. I went to a one teacher school in ah in (country town) and er I um went to er ah (sighs) from five till ah fifteen er seventeen. And then I went to (colloquial name of school).
Post-test 2	
Maybe you want to tell me about your childhood?	Childhood was 0 to 6 and at (coastal town) and 0 to 0 to yes er 6 to 10 in (country town). Er I don't know
What about your education?	I was at the school in (country town). I discovered that I was er in the er 6th form and er er I discovered that I was in the class of two classes, four to sorry. No No. 1 till 3 and 4 till 6 4 till 5
1 month follow-up	
I'd like to know something about your early life?	Ok um the ah um the early life er. From nought to six I was in ah ah (coastal town) and then from six till um I I was eh um (country town). And ah sorry. Five. Ah Then ah I used to ah er I um came to er (country town) in sorry ah ah 1950 ….er. No. 1939 …40 oh No Sorry.
What about your education?	Oh moved to (colloquial name of school) second form. Er Yeah yeah (long pause) No I

Table 2

Summary of CSN's structured interview across sessions

	Session					
	Baseline 1	Baseline 2	Baseline 3	Post-test 1	Post-test 2	1 month follow-up
Total						
Number of questions from SP targeting treated and untreated topics	10	9	8	9	9	5
Turns	15	7	11	13 (2 of which non-verbal)	15	11
Total words and fillers	70	14	98	125	146	140
Target words: type/token	1/1	0	2/3	1/1	1/1	1/1
Other content words: type/token	16/17	0	17/24	18/31	22/32	26/30
Closed class words	18	0	49	55	64	57
Yes/No	13	7	8	10	19	14
Fillers	21	7	14	28	30	38
Proportion content words	0.3	0	0.3	0.3	0.2	0.2
Words and fillers per turn	4.7	2.0	8.9	9.6	9.7	12.7
Content words (token) per turn	1.2	0	2.5	2.5	2.2	2.8
Treated topic						
Number of questions from SP targeting treated and untreated topics	6	5	4	5	5	5
Turns	11	5	9	8	10	11
Total words and fillers	61	11	95	113	122	140
Target words: type/token	1/1	0	2/3	3/3	1/1	1/1
Other content words: type/token	15/16	0	16/23	17/30	21/31	26/30
Closed class words	15	0	49	51	56	57
Yes/No	11	6	6	8	12	14
Fillers	18	5	14	23	22	38
Proportion content words	0.3	0	0.3	0.3	0.3	0.2
Words and fillers per turn	5.5	2.2	10.6	14.1	12.2	12.7
Content words (token) per turn	1.5	0	2.9	3.9	3.2	2.8
Untreated topic						
Number of questions from SP targeting treated and untreated topics	4	4	4	4	4	0 (interview discontinued)
Turns	4	2	2	5 (2 of which non-verbal)	5	-

KEY: SP = speech pathologist

Table 2, Continued

Summary of CSN's structured interview across sessions

	Session					
	Baseline 1	Baseline 2	Baseline 3	Post-test 1	Post-test 2	1 month follow-up
Total words and fillers	9	3	3	12	24	-
Target words: type/token	0	0	0	0	0	-
Other content words: type/token	1/1	0	1/1	1/1	3/4	-
Closed class words	3	0	0	4	8	-
Yes/no	2	1	2	2	7	-
Fillers	3	2	0	5	8	-
Proportion content words	0.1	0	0.3	0.1	0	-
Words and fillers per turn	2.3	1.5	1.5	2.4	4.8	-

DQI's performance was similar in pattern to CSN's. Her accuracy in picture naming increased from an average of 50% correct across pre-treatment baseline to 83% correct on the only post-test (Figure 3). There was a significant trend for improvement across the study from Baseline 1 to Post-test 1 for the treated set ($t(29) = 3.407$, p(1-tailed) = 0.001), but not for the untreated set in the treated topic ($t(29) = -1.608$, p(1-tailed) = 0.941) nor for the untreated topic ($t(61) = 0.247$, p(1-tailed) = 0.403). The change for the treated set was due to significantly greater improvement during the treated phase compared to the baseline (t(29)=3.233, p(1 tailed)=0.002), no such pattern was found for the untreated set ($t(29) = -1.859$, p(1-tailed) = 0.963). Moreover, there was a significant difference between the treated and untreated sets in the effects of therapy (p(2-tailed) < 0.001). At nine months post-treatment (with no ongoing practice), DQI's naming of the treated set returned to baseline levels, with performance on the untreated set within the treated topic and on the untreated topic unchanged over that period.

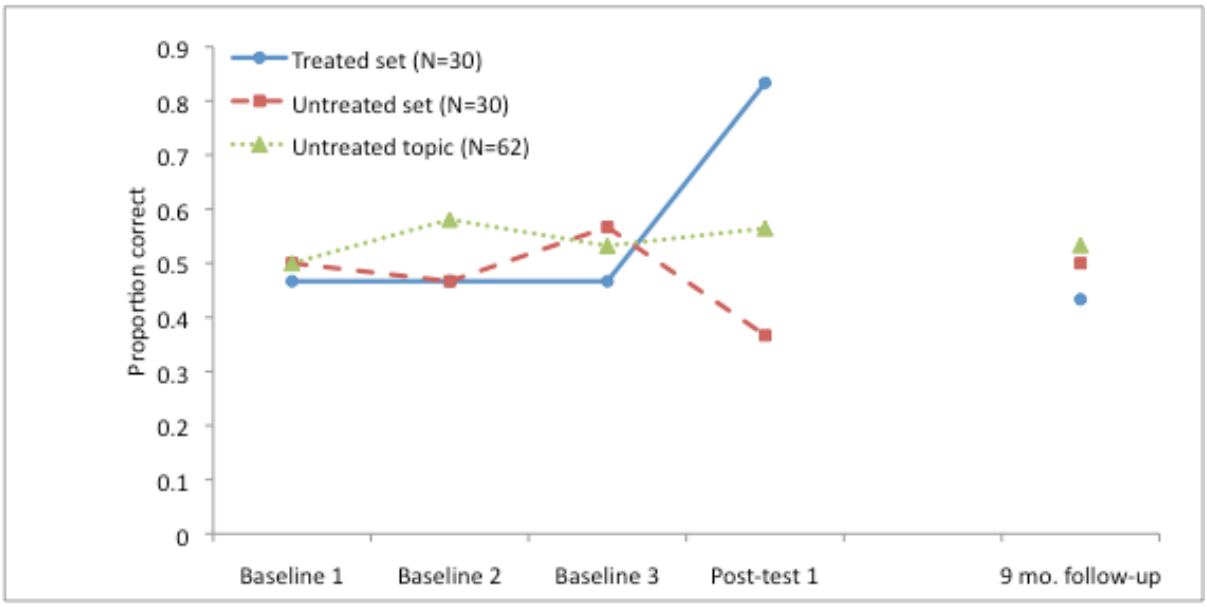

Figure 3. Proportion of pictures named correctly by DQI on each session.

DQI's improvement in naming did not translate to increased use of target words in the structured interview, and, like CSN, her use of treated words remained at floor across the study (Table 3 provides a sample of DQI's structured interview responses). DQI used five target words in the interview: "beach", "walk", "friends", "cake", and "yoga", and only "yoga," a treated word, appeared after treatment.

Table 4 summarises DQI's output in the structured interview across sessions. She showed no significant trends on any measure from Baseline 1 to Post-test 1, with the exception of a significant trend for decreased production of closed class words in the treated topic words, other content words (token), total content words (token) and closed class words for the combined topics and the treated topic alone, and for total words in the untreated topic. (Poisson test for trend using lambda coefficients for rate of change (WEST-Trend): all comparisons $z > 2.88$, and p(2-tailed) < 0.001). The contrast between the quantity of DQI's and CSN's contributions to the interview is also striking, reflecting the voluble spoken output typical in lvPPA compared with the sparse output typical of nfv PPA.

Table 3
Samples of DQI's responses to a question within the untreated topic (about activities around the house) across sessions in the structured interview.

Speech pathologist	DQI
Baseline 1	
Tell me about the things you do around the house on an average day?	Okay. I usually get breakfast and um clean the house. I'm not not probably the best housekeeper or anything like that but um and ah I do some gardening. And we walk. And um I don't know I just enjoy being in the house some though I sort of I go and do other things with other people and um I go and do some …I actually meant to bring a card down for you too but I didn't and so I might post one to you. My yeah cards that I make and things like that. And um. And I don't know and I sort of I have got friends that I go to and have lunch with. And things like that yeah sort of I get around a little bit
Baseline 2	
Tell me about the things you do around the house on an average day.	I get out of bed and um and then I do oh well I go and get breakfast and everything like that and then I do some housework and then I do some washing at some stage and then um oh. Then I Oh Isn't it silly um and then I do some gardening. And then I come in and do some cards
And that?	Make the cards And the I um make the do all the cutting and everything like that to do it and make certain things in the right place. My sister's not me told me er My sisters actually sort of she's really been into it for quite a while. And um so its good that way. And um and then I don't' know its about tea time
Baseline 3	
Can you tell me about the things you do around the house on an average day?	Ok On an average day…..its getting out of bed and um having breakfast with Dave and um and then we shower and then I'll start doing some work around the house. Sweep sweeping and vacuuming and things like that and then I um I do some work in the sense of you know, reading and and which I haven't told you that (HA hA) with reading and things like that so that um you know it just makes it a bit easier for me and things like that and then um by that stage its lunch time (laughs)and then I either go outside and do some gardening and um then I do some of my cards and
And this is…?	Mm yeah . And just sort of doing my papers and getting everything that I want to for the card and everything like that and And then probably I probably stop around 5 o o'clock so I do and then make dinner. And then we watch telly and then go to bed (laugh)
Post-test 1	
Can you tell me about the things you do around the house on an average day?	We oh well, we usually get up and we go for a walk um and we walk along the beach. And um and then we come home and have breakfast and we um I don't know. I hate doing this. Um And we do I don't know I do some oh some stuff outside around the house and everything like that and um and then we have meals and I think that's about it. I'm not very inventive at it either.
9 month follow-up	
Can you tell me about the things you do around the house on an average day?	OK, usually I um, we usually go for a walk in the mornings, on the beach and then we go home and we have breakfast or sometimes it's the other way around. And umm and we do a bit at the in the house so usually do some of the household and everything like that. And umm we hmmm.

Table 4
Summary of DQI's structured interview across sessions.

	Session				
	Baseline 1	Baseline 2	Baseline 3	Post-test 1	9 month follow-up
Total					
Number of questions from SP targeting treated and untreated topics	6	6	6	6	5
Turns	7	7	7	7	9
Total words and fillers	419	311	506	332	430
Target words: type/token	6/8	1/2	3/7	5/6	6/14
Other content words: type/token	37/46	31/42	63/84	41/52	53/67
Closed class words	322	232	366	224	306
Yes/No	5	0	4	3	9
Fillers	38	35	45	47	34
Proportion content words	0.13	0.14	0.18	0.17	0.19
Words and fillers per turn	59.9	44.4	72.3	47.4	47.8
Content words (token) per turn	7.71	6.29	13.00	8.29	9.00
Treated topic					
Number of questions from SP targeting treated and untreated topics	2	2	2	2	2
Turns	2	2	2	2	5
Total words	99	98	201	99	201
Target words: type/token	3/5	1/2	2/5	3/3	3/10
Other content words: type/token	10/10	9/10	24/33	12/16	21/29
Closed class words	74	73	144	65	143
Yes/No	2	0	0	0	4
Fillers	8	13	19	15	15
Proportion content words	0.15	0.12	0.19	0.19	0.19
Words and fillers per turn	49.5	49.0	100.5	49.5	40.2
Content words (token) per turn	7.50	6.00	19.00	9.50	7.80
Untreated topic					
Number of questions from SP targeting treated and untreated topics	4	4	4	4	3
Turns	5	5	5	5	4
Total words	320	213	305	233	229
Target words: type/token	3/3	0	1/2	2/3	3/4
Other content words: type/token	27/36	22/32	39/51	29/36	32/38

Table 4, Continued.
Summary of DQI's structured interview across sessions.

	Session				
	Baseline 1	Baseline 2	Baseline 3	Post-test 1	9 month follow-up
Closed class words	248	159	222	159	163
Yes/no	3	0	4	3	5
Fillers	30	22	26	32	19
Proportion content words	0.12	0.15	0.17	0.17	0.18
Words and fillers per turn	64.0	42.6	61.0	46.6	57.3
Content words (token) per turn	7.80	6.40	10.60	7.80	10.50

KEY: SP = speech pathologist

Discussion

This paper illustrates issues arising in the selection of functionally relevant stimuli for treatment, and in measuring generalisation from (successful) word retrieval treatment to word retrieval in functional connected speech, using case studies of two individuals with PPA.

We first considered whether a standard treatment for word retrieval disorders (RRIPP, Repetition and Reading In the Presence of the Picture) was effective with personally-relevant words in personally-chosen topics for two people with PPA. Both participants showed gains in naming treated items as a result of only 10 training episodes per item. One participant (DQI) showed larger gains than the other (CSN). We also asked whether the treatment gains reflected improvements in lexical retrieval rather than learned associations between the treated picture and the label. Both participants showed statistically significant gains when naming pictures different from those used in therapy. Hence the treatment was effective in improving naming, and reflected changes in the accessibility of treated words following treatment. Finally, we aimed to establish whether gains in lexical retrieval measured in picture naming would generalise to connected speech in a structured interview. Despite clear gains in lexical retrieval in picture naming, there was no significant increase in the use of treated (or untreated) stimuli in the structured interview, thus we observed no evidence of generalisation from the treated task to an untreated connected speech task in these two participants with PPA. We discuss the lack of generalisation below, but first focus on the treatment effects seen in word retrieval.

Treatment effects for personally-relevant words in personally-chosen topics in PPA

The improved picture naming by CSN and DQI following RRIPP treatment replicate the typical finding that therapy is effective when treatments are adapted from acute-onset aphasia for participants with PPA (Carthery-Goulart et al., 2013; Croot et al., 2009). Despite the neurodegenerative disease process, speech therapy can reduce impairment in people with PPA, thus, speech pathologists should consider treating people with PPA using all approaches, including impairment-directed approaches, consistent with their philosophy of therapy (McNeil & Duffy, 2001). Moreover, RRIPP treatment was effective with personally relevant words, many of which were longer and lower frequency than words typically chosen in research studies. The personal salience of the items we treated may have contributed to the participants' gains, consistent with the finding that better-known items benefit more from therapy in PPA (Jokel et al., 2014), and "trumping" the difficulty associated with increased length and lower frequency.

Lexical retrieval gains generalised to untreated pictures of treated stimuli for the two participants in this study, as reported previously in acute-onset aphasia (Howard et al., 1985). In the PPA literature, one individual with semantic dementia was able to name different exemplars of treated items (Heredia et al., 2009), while another was hampered by changes in the background colour of picture-naming stimuli (Snowden & Neary, 2002). Our results therefore suggest that generalisation to untreated exemplars of treated items, at least, is a realistic goal of therapy.

While not systematically manipulated, the stimuli encompassed a range of word types including common nouns, phrasal nouns (e.g. yoga mat), proper nouns (names of people and places), adjectives (e.g. hazy), adjective-noun phrases (e.g. pink sunset) and verb participles (e.g. cooking). Improvements were seen in the common nouns, phrasal nouns and adjectives, and in some instances in the other categories (but not reliably given the small number of items), but not in the proper nouns, which were named correctly before treatment. This extends previous research showing that RRIPP is effective for nouns and verbs, and suggests it may be possible to use RRIPP to treat other word classes (see also Renvall & Nickels, 2012). McNeil, Small, Masterson & Tepanta (1995) demonstrated treatment gains for adjectives using a cueing hierarchy for a man with progressive anomia, and Schneider, Thompson & Luhring (1996) demonstrated treatment gains for verb tense markers using a gestural plus verbal treatment, adding to the evidence that word classes apart from nouns are amenable to treatment in PPA. Intriguingly, in both

these studies there was also evidence for transfer to untreated items. The possibility that word classes other than nouns generalize more effectively remains to be systematically tested, and would be a logical extension of the work reported here.

CSN and DQI and those around them were generally positive about the treatment, and DQI often practised more than instructed. It was a limitation of our study that we had no systematic record of how much the participants practised, but it was likely there was more than one pass through the materials on some or most days. On the other hand, we had no doubt about the participants' motivation to participate and practise as required. We also received unsolicited feedback from a speech pathologist saying that a participant in the larger study, "benefitted from being a part of the research in so many ways not just improving her naming skills. It has given her a 'purpose' and has certainly improved her morale."

While word retrieval gains often persist over long periods for people with acute-onset aphasia (e.g. Nickels & Best, 1996; Pring, White-Thomson, Pound, Marshall, & Davis, 1990) people with PPA are more likely to lose gains than sustain them across a period of months if they do not continue the treatment activity (for reviews see Carthery-Goulart et al., 2013; Croot et al., 2009, Jokel et al., 2014). DQI declined between the post-test and the 9-month follow-up on picture naming, and we noted above the trend towards decline in treated items for CSN over six weeks after he ceased practising. This potential outcome, and the consequent need to persist with therapy over the long term, should be considered and discussed with participants prior to embarking on *any* impairment-directed treatment (Croot et al., 2011). Our approach is to recommend continued practice, both CSN and DQI began practising all words in the treated and untreated topics on their return from vacation after the study. CSN practised these for a further 6 months, until further disease progression (especially falls) led him to discontinue. Analysis of DQI's long term maintenance of all the target words is underway, and will be reported separately.

Assessing generalisation of gains in naming to connected speech

We found no generalisation of use of treated items to connected speech despite clear evidence of improvements in naming. We had hypothesised that when naming showed generalisation to untreated items, there would be gains in retrieval of these words in the structured interview. Given that neither CSN nor DQI showed naming generalisation, the lack of generalisation to the structured interview was consistent with our hypothesis. There were, however, positive changes that are harder to account for, as

has occasionally been reported in the literature. For example, CSN showed a trend toward increased words, content words and closed class words, although not only in the treated topic.

We selected the structured interview to assess generalisation to connected speech because it allowed us to direct the participant to talk about the treated and untreated topics. It also allowed us to standardise the elicitation of connected speech across sessions. Thereby, we hoped to reduce variability from session to session. Nevertheless we observed variability across sessions for most of the connected speech measures for both participants, which most probably were due to other factors. For example, as shown by CSN at Baseline 2, participants' motivation and engagement is impossible to control or standardise across sessions. There may be days when participation is difficult for personal or illness-related reasons (see further discussion of PPA-specific factors below), despite genuine commitment to the study and to treatment. Sensitivity, encouragement and flexibility by the clinicians interacting with participants will always be required to determine the best times to conduct pre- and post-treatment evaluations.

The nature of the structured interview format itself may also have contributed to the lack of generalisation to the interview. First, although we chose the interview as an analogue to conversation that we could repeat in a standard form across sessions, the very repetition of the questions removes the core communicative function of the answers after the first interview. The speech pathologist's introductions to the structured interview sometimes tacitly acknowledged this limitation, for example, she began one interview with, "Like last time, I want you to tell me…", and both participants said less on Baseline 2 than Baseline 1. It is also possible that the interview questions may have felt more like 'testing questions' than conversation, negatively impacting participants' motivation. Conversely, while the participants had less to say about the treated items (because the pragmatics of the interaction did not require that information previously communicated be repeated), the repeated elicitation of talk about the same topics, with the expectation that he participate in the conversation, led to increased production of other content (content words and closed class words) in CSN's case.

Third, while our topics and words were generated collaboratively, we remain uncertain whether the vocabulary selected for treatment was always the vocabulary required in the interview. For example, DQI's "hobbies and interests topic" included going to a café with friends, but when answering a question about this activity, she did not mention the "croissant", "cappuccino" or "frittata" she may typically order there, nor was

she pragmatically required to do so. This does not mean these words are not functionally useful, but they would be more useful when ordering in the cafe, than when answering a question about hobbies and interests[5]. Hence the difficulty for the researcher lies in selecting functionally relevant items (Renvall & Nickels, 2013a,b) that will be required in an interview or conversational topic. We originally intended to use the initial session with both carer and person with PPA to determine topics, words and interview questions, through a study of word retrieval failures, carer support and participant engagement. However, the volume of stimuli required for experimental rigour could not be generated by these means alone, such that the controlled elicitation of vocabulary remains a major problem in attempts to study generalisation to connected speech. The spouses of both CSN and DQI reported these participants were in fact using the treated items more in conversation after treatment (see also, Heredia et al., 2009), but it is difficult to interpret these comments in the absence of any systematic measure of the reported gains.

Sampling a range of other tasks that make fewer demands than a structured interview but greater demands than naming (e.g. sentence production, composite picture description, video description, narrative retell) may have revealed generalisation that was obscured by the demands of "thinking for speaking" in the structured interview. This could be investigated in future. However, it is important to be aware that such tasks can become another form of naming task, as some people with aphasia have a tendency to "hypername" rather than produce connected speech in such tasks (e.g. Cairns, Marshall, Cairns, & Dipper, 2007; Marshall & Cairns, 2005). For example, one woman, MM, when describing a picture of a woman driving a car produced ``my car…Ford Escort…blue [writes 'mirror']…and er Ford" (Marshall & Cairns, 2005, p. 1013). While these tasks may indicate ability to retrieve lexical items in response to a different stimulus type (picture or video) they cannot be said to measure generalisation into connected speech.

Beeke et al. (2011) discussed generalisation in treatment for agrammatism. They noted that outcome measures used to assess gains in conversation may be insensitive to change, or that task demands and language structures may be too different in everyday settings compared with constrained tasks in the clinic. Osgood (1949) first proposed that generalisation of learning would be predicted by degree of similarity of task and stimuli, and both are markedly different between our word retrieval treatment and conversation.

[5] We also asked DQI to imagine walking along a beach and to describe what she saw there, but this did not appear to result in retrieval of more treated or untreated words related this topic.

We may therefore have failed to observe generalisation of picture naming gains to the structured interview because the treated words failed to reach threshold for production due to competing demands associated with message formulation, syntactic formulation, monitoring one's own and others' contributions to the conversation, updating the discourse model and so on. To determine whether task demands in conversation account for the lack of generalisation we saw here, future researchers should design word retrieval interventions that reduce some of the cognitive load in the speaking task. For example, word retrieval in conversation may be supported by use of a communication book (Rogers, King, & Alarcon, 2000) including the treated words, or by therapies that train word retrieval or use of particular structures in interactive contexts which scaffold the acquisition and use of words in connected speech and conversation (Carragher, Conroy, Sage, & Wilkinson, 2012; Cartwright & Elliot, 2009; Herbert, Best, Hickin, Howard, & Osborne, 2003; Pulvermüller, et al., 2001).

Issues specific to people with progressive rather than acute-onset aphasia

It is also possible that issues directly related to progressive nature of disease in PPA made it difficult to measure gains in connected speech on the structured interview in this study. Here we raise a few of these for consideration. First, a key question is which aspect(s) of language it is appropriate to treat, or how best to maximise functional communication, at each stage of disease progression in PPA: a question best answered using a longitudinal design. People with PPA may, however, have other goals in the face of a prognosis of decline (such as travel plans, observed for both CSN and DQI in this study), or additional symptoms that emerge with disease progression (such as falls, as experienced by CSN), that preclude or restrict participation in a well-controlled, rigorously designed experiment.

Second, mood, and motivation for treatment may be lower in the context of progressive than acute-onset aphasia. CSN simply declined to answer questions about the untreated topic in the structured interview on more than one occasion. Third, adynamic features occur in a subset of people with PPA (Robinson, Shallice, & Cipolotti, 2005) who will therefore respond better in a more structured task (picture naming) than a less structured one (answering the question "Tell me about your job?"). In this study, CSN's adynamic presentation was evident in the initial discrepancy between his picture naming and spontaneous speech. Consequently, for adynamic individuals, conversation itself will need to become more structured over time. Their conversational partners may, by

necessity, choose to use more direct questions requiring limited output, while generalisation to unconstrained conversation or open ended interview questions may be an unrealistic and/or irrelevant goal. Measuring improved language production in highly constrained contexts may be more relevant. The investigation of generalisation to connected speech, and specifically, to a structured interview, is in the very early stages, thus it will be important to explore differences between individuals with different presentations in future studies.

Concluding comments

This is the first study to systematically investigate transfer to connected speech in a structured interview in PPA. Despite the lack of demonstrable generalisation of gains in treated items from picture naming to connected speech for these two individuals, it may be premature to conclude there is no benefit of treatment for communicative situations because of the difficulty of validly measuring any generalisation that occurs. Data from the additional participants in our wider study will provide further insight into the use of one particular task, a structured interview, to sample connected speech in PPA.

Taking a broader view, effecting transfer from impairment-directed interventions to activities and participation as described by the World Health Organisation International Classification of Diseases (WHO-ICD) has proven difficult across all domains of neuropsychological rehabilitation, not only in word retrieval or speech-language therapies (Whyte, 2002). Nevertheless, the goal of any impairment-directed treatment is, ultimately, to benefit everyday activities and contexts. We therefore need to understand the limits and the potential of word retrieval treatments to improve conversation in both acute-onset and progressive aphasia.

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APPENDIX

Stimuli for CSN

Treated topic (hobbies and interests): cooking, recipe, cookbook, limes, orange, rice, ginger, noodles, white wine, oil, capsicum, chicken breast, chives, snow peas, garlic, lemon, broccoli, onions, carrots, curry, parsley, coriander, red wine, risotto, scissors, knife, spoon, frypan, buffet, vegetable peeler, chopsticks, fork, stove, glasses, wok, camera, can opener, chopping board, reading, library, borrow, chapter, bookmark, nonfiction, index, illustrator, author, magazine, writing, fiction, bookshop, pages, novel, physiotherapy, walking, spine, yoga, tai chi, weights, beach, work, traffic, car, CD, names of four family members

Untreated topic (life memories): baby, student, family, lunch, photos, family tree, album, frame, hug, kiss, school, diploma, recorder, memories, steeple, pew, suit, tie, minister, church, stained glass, bible, choir, christening, Christmas, wedding, wedding rings, toast, birthday cake, candle, birthday party, gift voucher, decorations, present, card, lorikeet, seagull, balcony, view, CSN's occupation, names of two schools and eight localities, name of newspaper

Stimuli for DQI

Treated topic (hobbies and interests): beach, sand, rock pools, horizon, boat, bluebottles, jellyfish, shells, starfish, seaweed, dolphins, whales, waves, big surf, flat surf, foam, pebbles, rainy, sunny, clear, hazy, cloudy, high tide, low tide, towel, ocean baths, pink sunset, rainbow, bodyboarder, surfer, fishermen, bait, fishing rod, children, sandcastle, walking, sunscreen, sunglasses, umbrella, seagulls, Christmas, family, candles, wedding, cake, birthday, party, croissant, gym, yoga, yoga mat, water bottle, exercise, muscles, flat white, frittata, friand, wrap, cappuccino, friends

Untreated topic (around the house): kitchen, dishwasher, washing machine, dryer, stove, fridge, kettle, toaster, blender, vacuum cleaner, wok, saucepan, frypan, rice, pasta, noodles, steak, cereal, stir fry, salad, barbecue, sandwiches, casserole, baking dish, bread board, whisk, spatula, tongs, ladle, wooden spoon, can opener, colander, masher, alfoil (aluminium foil), gladwrap (plastic wrap), baking paper, bookcase, chair, coffee table, lampshade, tv, remote, rug, vase, kitchen, lounge, laundry, fence, hedge, path, washing line, shampoo, hair dryer, hairspray, massage oil, deoderant, perfume, moisturizer, lipstick, mascara, blusher, nail polish

Characteristics of stimuli

	CSN		DQI	
Word classes in treated & untreated topics				
Nouns	87		76	
Phrasal and compound nouns	18		34	
Proper nouns	16		1	
Verbs	3		0	
Verb participles	4		1	
Adjectives	2		5	
Adjectival noun phrases	0		5	
Total words	130		122	
Matching across sets within treated topic	Treated Set	Untreated Set	Treated Set	Untreated Set
Mean no. letters	6.9	6.8	7.4	7.2
Mean no. words	1.1	1.1	1.2	1.2
Mean no. syllables	2.2	1.9	2.2	2.0
Mean no. phonemes	5.4	5.1	5.9	5.6
Mean CELEX log frequency†	0.82	0.88	0.77	0.86
Mean CELEX spoken frequency†	0.65	0.66	0.53	0.54
No. correct Baseline 1	10	10	14	15
No. correct Baseline 2	13	11	14	14
No. pictures with description/cue	5	4	6	6

KEY: No. = number †Because items were personally relevant to the participants, frequencies were not available for all items. For phrasal nouns and two-word compounds, the frequency of the head noun was used. Compounds not listed in CELEX were given a frequency of zero.

Chapter 4

What's the evidence? Evidence for speech, language and communication interventions in progressive aphasia

ARTICLE:

Croot, K., Taylor, C & Nickels, L (2011) What's the evidence? Evidence for speech, language and communication interventions for progressive aphasia. *ACQuiring Knowledge in Speech, Language and Communication*, *13*(1), 38-41.

Author contribution statements for this article can be found in Appendix V.

What's the evidence? Evidence for speech, language and communication interventions in progressive aphasia.

Karen Croot, Cathleen Taylor and Lyndsey Nickels

Clinical scenario

You are the manager of the speech pathology department in a large metropolitan hospital with an outpatient rehabilitation service. A local geriatrician refers a 52 year old man with a diagnosis of progressive aphasia. You see him for initial interview and he reports a gradually worsening problem with talking that he first began to notice about 2 years ago. He has recently decided to take early retirement from his professional life as an architect because of the impact of these speech and language changes. His word finding difficulties and articulatory errors are readily apparent in conversation. He reports anxiety and frustration in speaking situations, and withdraws from communicative situations for fear of making errors. He speaks of wanting to be able to communicate, and is seeking treatment due to the distress and frustration caused by his communication impairment. Apart from his difficulties in speaking, he is in excellent physical health with no reported changes to his behaviour and personality or in his activities of daily living. He keeps up his hobby of kayaking, and has plans to travel with his wife. At the conclusion of the initial interview, you wonder what services you can offer to this client.

Response to this scenario

Your speech pathology team has previously assessed clients with progressive aphasia, provided education to clients and their families about the speech, language and communication changes that can be seen with the disease, and suggested ways to reduce associated activity limitations and participation restrictions. However you have seen a small but steady increase in the number of referrals for various progressive language impairments over the last few years, and have been thinking for a while that you would like to develop a management pathway that includes a more systematic approach to intervention. You are not sure what evidence is available to guide your decision-making.

Some health care providers question whether there is a place for interventions with this population, since there is currently no cure for the underlying neuropathological changes that cause progressive aphasia, and because the person's communication and cognitive abilities can only be expected to decline with disease progression. However, you

disagree with these views. You agree instead with McNeil and Duffy (2001), who advise that since a person with progressive aphasia has impairments similar to those seen in other adult neurogenic populations (including some with neurodegenerative disease), intervention *is* appropriate, guided by the same general philosophical, clinical, theoretical and practical considerations about treatment that you would apply in other neurogenic populations.

You also reflect that because there is an expectation of decline without treatment, the question about what intervention outcomes to expect in this client group is not straightforward. Although improvement above the level seen at initial assessment is one possible outcome if therapy is effective, it is not the only one. You might also see an outcome of no change (i.e. the client maintains his or her current level of ability), or a slowing of deterioration that allows the individual to continue in desired activities for a longer period of time than would have been possible without the intervention (Rapp & Glucroft, 2009). Education of the significant communication partner may also result in more successful communicative interactions both immediately and in the future.

Developing an answerable clinical question

To respond to this scenario you first develop an answerable clinical question using guidelines provided on a website promoting Evidence-Based Practice in Speech Pathology (http://www.ciap.health.nsw.gov.au/specialties/ebp_sp_path/resources.html) and within a previous "What's the Evidence Column" (O'Halloran & Rose, in press). These guidelines suggest you should first define the *patient or problem*, the *intervention*, the *comparison intervention*, and the *outcome*.

Patient or problem

"Primary progressive aphasia" is a broad diagnostic category in the sense that people with this diagnosis can have a diverse range of progressive language difficulties, sometimes accompanied by speech motor impairments (apraxia of speech, various types of dysarthria) and/or by other more or less severe cognitive impairments (e.g. memory problems). You realise that other diagnostic labels are used for people with progressive language impairments, such as semantic dementia, nonfluent progressive aphasia and frontotemporal dementia (and others, see Croot, 2009). To ensure that you pick up all of the relevant studies about intervention in this population you will have to search the scientific literature on a range of syndrome names and combine the results.

Intervention

Here you are willing to look broadly at what evidence there is for speech, language and communication interventions across this population, so you do not specify a particular type of intervention.

Comparison intervention

This is not relevant at this stage, because you're not yet trying to weigh up the effectiveness of one intervention against another, but rather to identify what the evidence is for any relevant interventions in order to decide what your service should offer.

Outcomes

The outcome (increased intelligibility, word retrieval, sentence comprehension, social participation etc.) would be determined by the type of therapy, and you are keeping your options open on type of therapy for the time being.

Clinical Question

The final clinical question you formulate is, *"What evidence is there to include speech, language or communication interventions in the speech pathology services provided for people referred with one of the types of progressive aphasia?"*

Searching for the evidence

The first databases you search are *Medline*, *PreMedline*, and *PsychINFO* and the database of *Cochrane Reviews*. These are all available via the *Ovid SP* gateway, which means they can be searched at the same time. Because the search engine can remove duplicates if you select this option, this is more efficient than searching the 4 databases serially. Table 1 outlines the keywords that were generated and searched to find any relevant literature.

You limit your search to English language papers and human studies (in order to exclude research on drug therapies tested in animal models). Because you have designed your search to be exhaustive in identifying possible evidence-based treatments, it retrieves 457 studies. Many of these, however, describe experimental pharmacological interventions or pathological mechanisms, rather than speech, language or communication interventions. By listing the results by title, 100 per page, it is possible to scroll through to identify only the speech-language pathology interventions. You find a critical review of all intervention studies published to mid-2007 (Croot et al., 2009), a review of anomia treatment in semantic dementia (Henry et al., 2008), and the 7 further studies in Table 2.

Table 1: Search terms

PICO	Search Terms	Notes
Patient or Problem	"progressive aphasia" "progressive non fluent aphasia or progressive non-fluent aphasia" and "semantic dementia" and "fronto-temporal dementia or frontotemporal dementia or frontotemporal lobar degeneration"	Multiple search terms were required given the different labels for progressive aphasia that exist in the literature.
Intervention	"intervention or treatment$ or therap$"	$ indicates that the search term is truncated. The search engine will pick up any words starting with that letter string (e.g. therapy, therapies, therapeutic).
Comparison Intervention	No search terms	You are interested in any interventions done with this clinical population.
Outcomes	No search terms	You are interested in any treatment outcomes.

Next you search the *SpeechBITE*™ database that catalogues published speech pathology interventions, searching on the term "progressive aphasia" and scanning articles listed for the client subgroup "Alzheimer's and other dementias", which yields one additional study, not yet pre-appraised. Search results are summarised in Table 2, and rated for Level of Evidence according to the NH&MRC Levels of Evidence Hierarchy, where level I represents the highest level of evidence and level IV the lowest (NH&MRC, 2009).

Table 2: Research articles identified.

Articles identified	Purpose	Level of evidence (NHMRC, 2009)
Diehl et al. (2003)	Pilot support group for spouse-carers of people with frontotemporal dementia, reports survey of carers after group	Not applicable
Henry et al. (2008)	Semantic treatment for anomia in progressive vs. stroke-induced aphasia	IV
Rogalski & Edmonds (2008)	Attentive reading and constrained summarisation (ARCS) treatment to promote intentional language use and attentional focus to improve discourse in a man with PPA	IV
Newhart et al. (2009)	spoken naming therapy using a cueing hierarchy in 2 cases, one logopenic progressive aphasia and one semantic dementia	IV
Robinson et al. (2009)	Therapy naming, defining and using objects in 2 individuals with semantic dementia	IV
Jokel et al. (2010)	Computer-based treatment for anomia in semantic dementia	IV
Taylor et al. (2009)	Reports a survey of PPA referrals to NSW speech pathologists and services provided	Not applicable
Henry et al. (2008)	Reviews anomia treatment in semantic dementia	Reviews a mix of Level IV studies and others
Croot et al. (2009)	Reviews published impairment- and activity / participation-directed interventions in semantic dementia and progressive aphasia	Reviews a mix of Level IV studies and others

KEY: PPA = primary progressive aphasia

You read over the summary of cases reviewed by Croot et al. (2009, Appendix) and the abstracts of the additional articles, to identify individuals similar to your current client. The findings are provided in Table 3.

Table 3: Cases similar to your current client. KEY: F = female, M = male

Authors	Case Description	Intervention
Jokel et al. (2009)	F, 58 years, 3-4 year history of nonfluent aphasia, slow and anomic speech	cued naming treatment to improve retrieval of nouns
McNeil et al. (1995)	M, 61 years, lawyer with 9 month history or anomia, mild spastic dysarthria, and mild aphasia	hierarchical cueing of synonyms and antonyms to improve retrieval of adjectives
Schneider et al. (1996)	F, 62 years, nonfluent aphasia (anomia, slow, agrammatic speech, pronunciation errors)	gestural combined with verbal forms to promote use of nouns, verbs and tense markers
Cress & King (1999)	M, 60 years & F, 59 years with 6-7 year histories of nonfluent speech	AAC: communication boards, books and file cards
Pattee et al. (2006)	F, 57, primary progressive aphasia with apraxia of speech	text-to-speech and American sign language
Rogers et al. (2000)	M, 71 years, 2-year history of anomia, AOS and telegraphic speech	principles of proactive intervention, AAC
Cartwright & Elliot, (2009)	F, 65 years, F, 59 years, and F, 66 years with increasingly nonfluent speech, with social disinhibition, pronounced anomia and agrammatic output respectively	group programme with aphasia-friendly TV viewing to promote discourse comprehension and production

You notice some things in common across these studies, with the controlled impairment-directed interventions producing a treatment effect in all cases but almost no generalisation. Furthermore treatment gains are not well-maintained once therapy ceases. The activity and participation-directed interventions are reported to be successful in helping the participant achieve desired social and communicative goals, but these reports are case descriptions not controlled studies. You select the article by Jokel and colleagues as appropriately similar to the potential new referral and critically appraise the study following the EBP guidelines: http://www.ciap.health.nsw.gov.au/specialties/ebp_sp_path/resources.html (Table 4).

As the paper reports a single case design you also evaluate the methodology of the paper using a scale for rating Single Case Experimental Designs (SCED; Tate, McDonald, Perdices et al., 2008). The method received 8/10 points for clear identification of target behaviours, overall design (multiple baseline across behaviours), establishing a stable pre-treatment baseline, sampling during treatment, providing raw data in a graph, use of statistics, replication across two individuals, and testing of generalisation. The 2/10 points that were not awarded were for independence of assessors and inter-rater reliability. However, given the nature of the outcome measures (naming accuracy) you feel this is not too great a problem.

Clinical bottom line

Having surveyed the literature you return to your clinical question and determine the clinical bottom line:

There is Level IV evidence for the efficacy of word retrieval interventions for treated items in progressive aphasia and semantic dementia

Some of these were studies that rated highly on the Tate et al. (2008) SCED scale, indicating methodological adequacy for single case designs. Hence, these provide some basis for clinical-decision-making in your service, taking into account the similarity of presenting clients to participants described in the published studies. However, there are no randomised control trials and almost no replications of the same treatment with different individuals that would indicate the generality of the results for any intervention, thus at this point in time, every intervention would need to be considered experimental.

Table 4: Critically appraised article

Article title	Relearning lost vocabulary in nonfluent progressive aphasia with MossTalk Words®
Citation	Jokel, R., Cupit, J., Rochon, E. & Leonard, C. (2009). Relearning lost vocabulary in nonfluent progressive aphasia with MossTalk Words®. *Aphasiology*, *23*(2), 175-191.
Design	Case series pretest posttest
Level of evidence	NHMRC: IV Tate et al (2008): 8/10
Participants	2 people with nonfluent progressive aphasia, one slow and anomic, the other hesitant and anomic
Experimental group	Cued naming of 3 lists of 14-15 words, 1 hour 2-3 times per week for 4 weeks (participant 1) and 12 weeks (participant 2) using MossTalk Words®, a computer-based therapy with a large array of words with pictures and cues including high frequency items.
Results	Improvement on all 3 treated lists by both participants, maintained at 1 month with no practice but not at 6 months. No generalisation to a 180-item picture naming test but improved syntactic production at 1 month but not 6 months post treatment.
Summary	Two individuals with anomia in the context of nonfluent progressive aphasia improved word retrieval for treated items that did not generalise to untreated items but improved syntax in a sentence production task.
Clinical Bottom line	Word retrieval can be improved with treatment in nonfluent progressive aphasia, but improvement is likely to be restricted to treated items and may not be maintained when therapy activities cease.

There is limited evidence for other interventions

For example, there is no evidence for an impairment-directed intervention that targets apraxia of speech in this population, and predominantly anecdotal evidence for the success of activity/participation-directed interventions.

Collaborative decision-making and goal-setting with client and significant communication partner(s) is necessary

Collaborative decision making is required when deciding whether to proceed with an impairment-directed or an activity/participation-directed intervention and about selection of words to target in treatment given lack of evidence for generalisation. Consultation will also include full disclosure to the client and communication partners about the limits to the evidence that any therapy will work, the need to rehearse to maintain any relearned vocabulary, the eventual loss of learning with disease progression, and the fact that the aim of therapy is to maintain current abilities or slow decline, not return to previous levels of function.

Regular review

Some people with progressive aphasia have deteriorated rapidly, within 1-2 years, while others maintained very good communicative abilities over 8 or more years (Croot, 2009). Therefore regular reviews will be essential, and it will be important to discuss with the client the need to proactively manage anticipated decline (Rogers & Alarcon, 1998).

Conclusion

Can your service offer an evidence-based approach to intervention in progressive aphasia? In your view, the limited empirical evidence suggests that intervention may appropriate. Hence you conclude that for each case you will base your clinical decision-making on the combination of the best currently available evidence, your own clinical expertise, and the client's values (Harasty, 2010).

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Chapter 5

Treatment for lexical retrieval impairments in primary progressive aphasia: A research update with implications for clinical practice

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Abstract

Lexical retrieval impairments (also known as anomia or word-finding deficits) are an early and prominent symptom in primary progressive aphasia (PPA), causing distress and frustration to individuals with PPA and their communication partners, and prompting research on lexical retrieval treatment. This paper reviews the research on lexical retrieval treatment in PPA from the earliest reports in the 1990s to early 2018 and considers the implications of this research for clinical practice. The number of published studies has increased markedly over the past decade, consisting primarily of behavioral studies, with rapid recent growth in non-invasive brain stimulation studies. Five general treatment techniques were identified in the behavioral studies, described here as standard naming treatment, Look, Listen, Repeat treatment, cueing hierarchies, semantically-focussed treatments, and lexical retrieval in context. Across techniques, behavioral studies targeting difficult-to-retrieve items typically report immediate gains, and there is evidence these gains can be maintained over months-to-years by some participants who continue with long-term treatment. There is also evidence that prophylactic treatment supports retrieval of treated items compared with untreated items. There is limited evidence for generalization of treatment to untreated items, suggesting the primary aim of lexical retrieval treatment in this population is to maintain retrieval of a core vocabulary for as long as possible. Language and cognitive assessment and piloting of the intended treatment can inform decisions about treatment selection and participant suitability for long-term lexical retrieval treatment. The paper concludes with some questions to guide clinical decision-making about whether to implement or continue with a behavioral lexical retrieval treatment.

Keywords: semantic dementia, word relearning, speech therapy, cognitive intervention, review

Interventions for lexical retrieval impairments in primary progressive aphasia: A research update with implications for clinical practice

The neurodegenerative diseases that cause dementia present with clinical symptoms determined by the distribution of pathological changes in the brain, and the function of the regions affected by those changes[1]. The diseases on the frontotemporal lobar degeneration (FTLD) spectrum as well as Alzheimer's disease can target brain regions that participate in speech, language and communication networks[2]. The symptoms may be relatively selective to speech and/or language in the early stages, but as the pathology increases and spreads in the brain over time, changes may extend to other aspects of cognitive, behavioral, emotional, and motor functioning[3]. The heterogeneous clinical syndromes that result are known under the collective name of *primary progressive aphasia* (PPA). Since the first reports of PPA, lexical retrieval impairments (also known as anomia or word-finding deficits) have been noted as one of the earliest-appearing and most prominent symptoms in PPA[4]. These impairments can occasion distress and frustration to the individuals with PPA and their communication partners, prompting research on lexical retrieval treatment.

This paper provides an update on lexical retrieval treatment in PPA from the earliest reports in the 1990s until the end of January 2018, with implications for clinical practice. The first section of the paper introduces key questions about the clinical benefit of lexical retrieval treatment in PPA that were raised by the earliest studies and have remained current over the intervening years. The second section describes the increased research on lexical retrieval treatment in PPA over the past decade and considers its quality. The third section identifies the main behavioral techniques used this research, asks whether there is any evidence that some treatments are more successful than others, and

notes the implications of this research for lexical retrieval treatment in the PPA clinic. The fourth section briefly describes recent advances in the use of non-invasive brain stimulation techniques to treat lexical retrieval impairments in PPA. These techniques are still in the early stages and not yet ready for widespread adoption into clinical practice. The paper concludes with some questions to ask when deciding whether to implement a behavioral lexical retrieval treatment in clinical practice with individuals with PPA.

Questions about the efficacy and priority of lexical retrieval treatment in PPA

The World Health Organization's classification of functioning, disability and health[5] describes *impairment-directed interventions* aimed at remediating physiological or psychological functioning of body structures (brain and psycholinguistic processes respectively), as well as *activity/participation-directed interventions* supporting the individual's ability to carry out a desired activity or participate in a specific life situation. In an earlier paper[6], we reviewed 23 studies reporting 33 participants in total: almost half the studies reported impairment-directed behavioral interventions targeting lexical retrieval using the types of speech language therapy tasks also used with non-progressive aphasia[7]. One further study reported a pharmacological plus behavioral intervention, another described a pharmacological trial, and one was a non-invasive brain stimulation intervention. The critical questions in these early impairment-directed studies were whether treatment produced immediate gains[†], whether those gains generalized to untreated items, activities or settings, and whether any gains were maintained after treatment activities ceased.

The most striking – and perhaps even surprising – finding in the context of progressive disease was that immediate treatment gains were reported for all individuals in

[†] Defined as changes in the behavior targeted by the treatment immediately after the period of treatment, also described as "direct treatment gains"[8,9].

the behavioral studies, regardless of the type of intervention used or the clinical presentation of the participant, with one exception[10]. There was no additional benefit of combined pharmacological and behavioral treatment over behavioral treatment alone in the one study that compared these[11], and results were mixed in both the pharmacological trial[12] and the rTMS study[13]. Behavioral interventions delivered reliable immediate gains, and it was impossible to determine from the scant evidence about the other interventions whether they might yield larger, more generalized or longer-lasting gains. The results for generalization and maintenance of immediate gains in the behavioral treatment studies were less positive. Only two reported generalization to untreated items or settings[11,14], and treatment gains declined over two months to a year after the participant ceased treatment activities, except for one individual who maintained her gains for 8 months[14].

Our first review concluded that a diverse range of techniques adopted from speech-language therapy for non-progressive aphasia were likely to yield immediate gains in lexical retrieval across different clinical presentations of PPA. It cautioned that improvement would be greatest for – or perhaps even unique to – treated items, and unlikely to be maintained over six months once treatment stopped. It raised questions about the adequacy of treatment designs in some studies, the treatment and participant characteristics that best predicted treatment outcomes, and the treatment mechanisms. Despite the many open questions, the implications for clinical practice were that lexical retrieval treatment should be introduced if this was best suited to a client's individual needs and goals and a therapist's philosophy of treatment[7]. It should target highly functional, personally-relevant words in anticipation that only treated words may benefit from treatment, and should be ongoing until words could no longer be maintained by treatment in the context of language decline.

Subsequent reviews concurred with these conclusions[15,16,17]. In 2011, a set of consensus criteria were developed to improve uniformity of PPA case reporting and reliability of results across studies[2]. These differentiated three clinical variants of PPA on the basis of language profile and regions of brain abnormality on imaging. The *nonfluent/agrammatic variant* (nf/avPPA) is characterized by apraxia or speech and/or agrammatic language, with diagnosis supported by fronto-insular imaging changes. The *semantic variant* (svPPA, also known as semantic dementia) is characterized by impaired naming and comprehension in the context of anterior temporal changes. The *logopenic variant* (lvPPA) is characterized by impaired word retrieval and sentence repetition, and supported by left posterior perisylvian or parietal changes. In one systematic review of 40 individuals with PPA[18] there was good evidence for lexical retrieval treatment in svPPA, but insufficient investigation of lexical retrieval in nf/avPPA and lvPPA to recommend lexical retrieval treatment in the latter two variants, despite reported treatment gains.

Despite the qualified endorsement of lexical retrieval treatment for PPA in these reviews, there were reasons to question the priority of lexical retrieval treatment in the PPA clinic[19]. First, the evidence is weak in some cases, due to limitations in the internal and external validity of some studies[20]. Many studies that report a successful treatment outcome have not included sufficient experimental control to unequivocally attribute a post-treatment improvement to the intervention. For example, studies may have conducted only one pre-treatment measure, failing to control for repetition/practice effects, or they may have failed to apply an appropriate statistical test when this was needed to establish that the observed results did not arise by chance[21]. Further, although small-n studies are typical of cognitive rehabilitation research in the early stages[22], some researchers called for more replication of treatment outcomes[20]. Finally, even in the better-designed studies there was minimal investigation of the impact of lexical retrieval treatment on functional

language use[20], or connected speech or discourse production[23], raising the question of whether lexical retrieval treatments actually benefit participants in their everyday lives. In view of these limitations, some clinicians and researchers have concluded that activity-participation and psychoemotional interventions are better clinical choices for this population, incorporating communication partners, emotional support and individualized strategies to assist with everyday activities and communication challenges[19].

Overview of lexical retrieval treatment in PPA in the research literature

To explore how the ongoing research into lexical retrieval treatment in PPA might inform clinical practice, the following discussion reviewed 81 studies[24] published since 1995 that either directly targeted lexical retrieval, or that targeted language, cognitive or brain functioning, with lexical retrieval in naming (picture naming, action naming, naming to description) or word generation tasks (letter or semantic category fluency) as a primary outcome measure[†]. See Appendix I for more information on the search strategy and articles identified. A number of important trends were immediately apparent (Figure 1). First is the substantial growth in treatment studies for lexical retrieval in PPA over the past decade. The majority of interventions still utilize behavioral treatment alone, but there has been recent growth in non-invasive brain stimulation (rTMS, tDCS) studies. Pharmacological studies continue to be rare, reflecting the absence of disease-modifying agents for FTLD and Alzheimer's disease[25]. The number of new participants reported in behavioral interventions each year has increased from a trickle until 2008 to an average of 14 per year from 2009 onwards (Figure 2a). The spike in reported cases in 2016 reflects a cohort of 21 individuals in a single study who received lexical retrieval alone or in

[†] Conference proceedings (single- paragraph as well as multi-page abstracts) were included to capture research not yet published in a full paper. Interventions for speech motor control or spelling were excluded, unless these were conducted alongside treatment for lexical retrieval. Published conference abstracts superceded by a full paper were also excluded.

combination with treatment for motor speech disorders via an online treatment platform[26]. This one data point highlights the way new technologies are extending the reach of treatments to this rare clinical group.

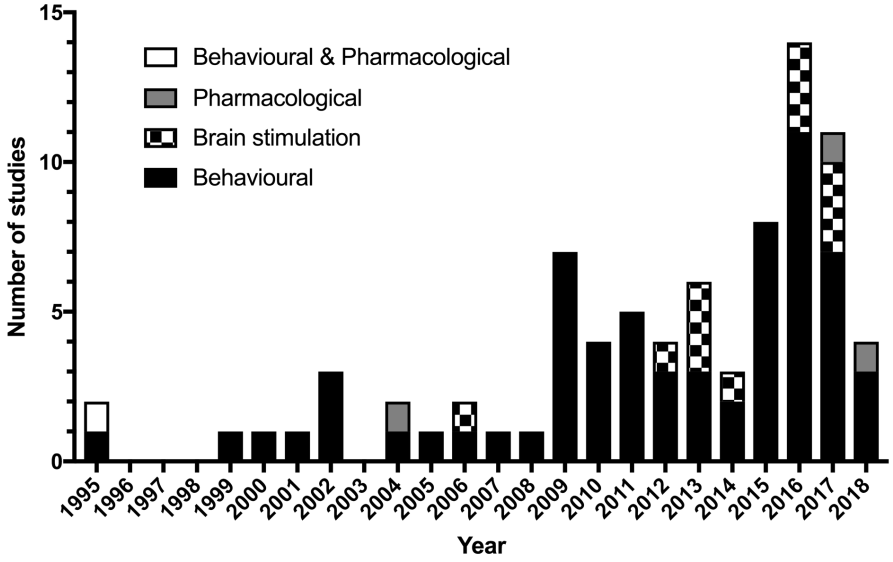

Figure 1. Number of treatment studies per year by treatment type.

There are close to a third as many unique participants in the non-invasive brain stimulation studies as in the behavioral studies (Figures 2a, 2b), a large proportion given the relatively recent development of rTMS and tDCS technologies. Around 80% of participants receiving non-invasive brain stimulation have nf/avPPA (Figure 2b), in contrast with the behavioral studies, where around 50% have svPPA, and roughly equal percentages of participants with nf/avPPA, lvPPA, and PPA not otherwise specified make up the balance (Figure 2a).

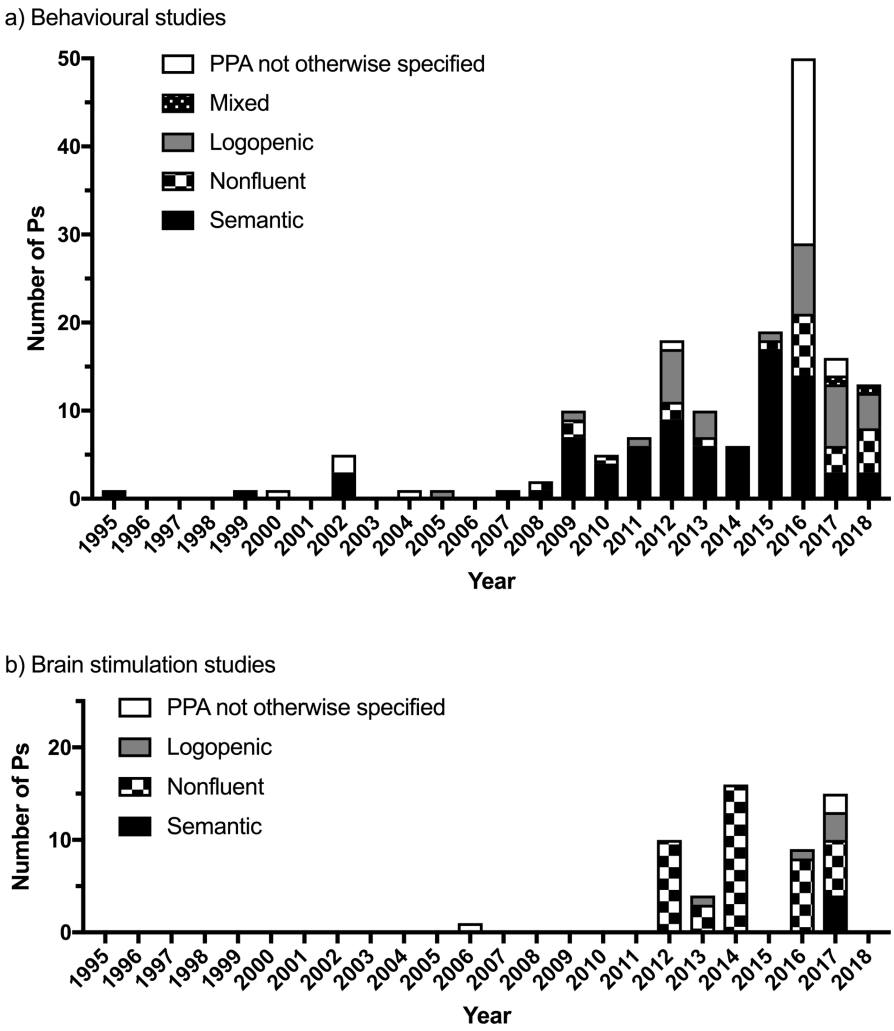

Figure 2. Number of new participants reported per year by PPA variant in (a) behavioral treatment studies and (b) non-invasive brain stimulation studies. Counts exclude individuals noted or judged likely to have been reported in an earlier study.

The quality of the evidence about behavioral lexical retrieval intervention has increased along with the number of studies. Until 2008, all studies were single case designs with a maximum of two participants, whereas in the last decade research teams have begun reporting case series of 8 to 10 individuals[27,28,29,30] as well as group studies with 7 to 26 participants[31,32]. These represent good progress in replicating the same intervention across larger numbers of participants, augmented by multiple reports of similar treatments investigated by different groups. We can now identify the frequently-

used treatments and ask how they compare with each other, as described below. Beales et al.[17] found, however, that none of the lexical retrieval treatment studies they reviewed met all recommended criteria for safeguarding internal and external validity in single case experimental design studies[33]. This "report card" shows there is room to improve the quality of our single case experimental design treatment studies, and cautions us to continue critiquing the findings of these studies before translating them into clinical practice. On the positive side, it demonstrates that many studies are now addressing the methodological weaknesses of the earlier research, providing better information about the efficacy and limits of lexical retrieval treatments in PPA.

Immediate gains, generalization and maintenance of gains in behavioral studies

Despite the apparent diversity of behavioral treatments reported, the procedures across studies can be grouped into five general techniques. The first is described by some authors[34] as "standard naming treatment", starting with an attempt to name the picture, followed by a prompt or the picture name if the initial attempt is not successful. The second is reading and repeating the name of the target item in the presence of a picture of that item[29], described by Savage and colleagues[35] as "Look, Listen, Repeat". In a variant of this treatment that enriches the semantic content of the materials, a personally-relevant description of the target or other semantic information is also presented[36, 37]. The third technique comprises cueing hierarchies incorporating a series of semantic and/or phonological and/or orthographic cues[8,11,38,39], with additional retrieval practice in a variant of this technique[9,40,41]. A fourth "semantically-focussed" technique concentrates on elaborating the semantic features or associations of the target item[34,42]. In a variant of this technique, participants are also trained with a strategy to assist with lexical retrieval[9,43,44]. A fifth group of studies elicit "lexical retrieval in context", eliciting the target a larger unit of language production, in sentence completion, sentence production, or discourse

production tasks, with the aim of generalizing treatment gains beyond the single word level[23] and to functional contexts[45]. The overwhelming majority of well-designed studies continue to report statistically significant treatment effects across participants and techniques: Is there any evidence to suggest that some of these techniques are likely to be more or less successful than the others in the clinic?

Comparison of lexical retrieval treatment techniques within studies

The first potential source of evidence is the small number of studies that compare different techniques head-to-head within the same study (and the same participants). For example, Jokel and Anderson[31] found better lexical retrieval by a group of seven individuals with svPPA after treatment with a semantic and phonological cueing hierarchy when the treatment was errorless than when the individual was asked questions and able to make errors in responding. There was some generalization to untreated items, and the immediate gain was higher for words for which the participants had some residual semantic knowledge (demonstrated in accurate word-picture matching).

Savage and colleagues[35] compared a Look, Listen, Repeat plus description treatment with a lexical retrieval in context treatment combining Look, Listen, Repeat with a sentence-generation task with two individuals with svPPA. Immediate gains were higher for words treated with the additional sentence generation exercise, but the maintenance effects were less clear. These researchers then compared Look, Listen, Repeat without the description with Look, Listen, Repeat plus sentence generation carried out by a third individual with svPPA, and both conditions produced a significant immediate gain that was maintained at 2-month follow-up. Savage et al concluded that the semantic description was not critical to the immediate gain or its maintenance when participants had partial semantic knowledge of the treated items, but that the role of the sentence-generation task required further investigation.

Suárez-González and colleagues[34,42] followed up the work of Savage and colleagues by comparing a semantically-focused treatment called "Conceptual enrichment therapy", or COEN, with a standard naming treatment, for items that two individuals with svPPA were unable to either name or describe (suggesting the semantic representations for these items were substantially compromised). In COEN treatment, target pictures were presented with two further pictures ("co-targets") that were conceptually-related to the target in a personally-relevant way for each individual. The aim of the co-targets was to rebuild and enrich the semantic network for the semantically impoverished items. A personally-relevant description linking the three pictures was presented verbally on the first treatment session in both conditions. For both individuals, the immediate gain (from zero correct) was around 80-90% in both treatment conditions (more than 150 items in one case[42]), with object description and naming to description better after COEN, showing generalization of learning to other tasks.

Krajenbrink and colleagues[46] conducted a study comparing three treatments with a man with svPPA. Look, Listen, Repeat treatment yielded greater immediate gains when treatment also incorporated written responses than when treatment required spoken responses only. There was no immediate treatment effect with COEN. Another brief report comparing picture-word association training and multimodal treatment for semantic knowledge and naming in three individuals with svPPA found no difference between the two techniques[47].

To date, head-to-head comparisons of these general treatment techniques have only been conducted with people with svPPA. There is no strong evidence in these comparisons that picture naming improves more in a semantically-focused task than a Look, Listen, Repeat task. It has been suggested that immediate gains in naming may be associated either with a strengthening of residual semantic representations/networks[34,42] or the

recruitment of right hemisphere homologues of left hemisphere regions[37,48], and that gains are greater when an individual has partial semantic knowledge of the to-be-treated items[15]. Alternatively or additionally, gains may be associated with the recruitment of relatively preserved lexical-phonological processing[39]. The advantage shown in Look, Listen, Repeat treatment with written responses over COEN treatment by Krajenbrink and colleagues[46] may reflect this individual's ongoing strengths in written over spoken language production.

The clinical implication of this body of research is that lexical retrieval treatment that capitalizes on an individual's residual lexical and cognitive strengths is likely to produce the best outcomes. Graham and colleagues[10] proposed that participant DM's gains in verbal fluency tasks in the context of the extensive atrophy in anterior temporal regions seen in svPPA were likely due to preserved functioning of medial temporal memory structures. According to complementary learning systems theory[49], newly-learned information (such as that acquired during lexical retrieval treatment) is initially supported by memory systems in the medial temporal lobe and later consolidated to the neocortex. Where the neocortex is compromised by neurodegeneration in PPA (primarily in anterior temporal regions in svPPA; in other cortical regions in the other variants), consolidation of new learning to those cortical regions will also be compromised[30]. Memory consolidation will be positively associated with the functional integrity of brain tissue in those regions[27], predicting better treatment outcomes when there is milder disease. There is still a question mark about the importance of errorless learning, the benefits of which were directly demonstrated by Jokel and Anderson[31], but which are also indirectly seen using Look, Listen, Repeat techniques[37]. Several cueing hierarchy treatments do not use errorless approaches and nevertheless demonstrate reliable gains[9,39]. It may be that the wide variety

of lexical and cognitive systems recruited across the diverse activities in cueing hierarchies offset the costs of occasional errors.

Comparison of lexical retrieval treatment techniques across studies

A second source of evidence on the question of whether any one technique yields the greatest benefits in treatment would come from a comparison of immediate gains achieved using different techniques. A statistical analysis of these gains is far from straightforward because of differences in reported measures from study to study, as well as contradictory opinions on how such gains can be aggregated[50,51]. Nevertheless, we can make some preliminary comparisons estimating the raw numbers of items gained across studies using different techniques. In our own recent studies, a heterogeneous convenience sample of individuals carried out a Look, Listen, Repeat treatment in one or more two-week phases[30,46]. Three participants with marginally significant gains (one nf/avPPA, one mixed PPA and one svPPA) acquired approximately 5 or 6 items from baseline to post-treatment, whereas two individuals with nf/avPPA with statistically reliable gains increased their total correct by approximately 15 items. While the number of items gained in any single phase was low, all four individuals who completed multiple phases of treatment continued to add words with each treatment phase, up to 35 and 40 previously-unnamed items for the two (nf/avPPA) participants who made the greatest gains. Similar results are shown in other multi-phase studies using Look, Listen, Repeat techniques[35].

We can compare these results with those obtained using Lexical Retrieval Cascade[9], a well-described cueing hierarchy technique that has also been investigated in a number of studies[40,41]. Small sets of approximately 5 or 6 items are treated intensively in each session, with the participant moving onto a new set when they reach a predetermined accuracy criterion (e.g. 80% correct). Lexical Retrieval Cascade studies show immediate gains after only a few sessions of treatment, a frequently-reported pattern[52,53], thus over

successive sessions, new sets can be introduced and mastered. Participant CT2 (lvPPA) acquired the majority of the 36 items treated across 6 successive sets[40], and Participants SV, LV[9] and P1[41] each gained close to 5 items per set across successive sets, raising the intriguing question of how many items could potentially be added by serially treating additional sets.

Home treatment carried out by an individual with svPPA sheds some light on this question[54]. She used computer flashcard software combining semantically-focussed and standard naming techniques. Approximately 35 items were treated per half-hour session, three to four times a week. An algorithm in the software determined frequency of presentation for practice on the basis of the participant's self-rated accuracy, with low-accuracy items presented more often. This individual was highly motivated, and learned to make her own flashcards for personally-relevant words. Over 20 months she developed 591 flashcard items and learned 139 of these well. Better-learned items were the ones introduced in the first half of the treatment period, consistent with better preserved semantics and longer treatment yielding greater benefits, but even item names that were "forgotten" after successfully being treated could be restored again with further practice. The same ability to restore items forgotten after treatment has also been shown in a single case series of 9 individuals with svPPA[27]. Participants were treated using two sets of approximately 30 items each (around half of which could still be named) with a Look, Listen, Repeat technique for 20 minutes per day, five days a week for 8 weeks such that most words were correct immediately post-treatment. When accuracy fell below 80%, the researchers introduced "revision practice" (approximately 2 sessions per week) to restore accuracy to 80% or above. Less revision was needed by individuals with less severe disease.

In both these studies, time spent in treatment was optimized by ceasing treatment for items at criterion level, monitoring their accuracy, and re-instituting treatment (revision practice) once accuracy fell below criterion. Such monitoring has the further advantage of indicating when accuracy and immediate gains are declining despite ongoing treatment activities, prompting the introduction of intervention approaches suited to more advanced disease. In the current literature, smaller sets of around 5 items treated intensively with a rich cueing hierarchy for up to an hour per session have shown immediate gains over periods of a few days or a few treatment sessions, and sets of 30 or so items treated with a Look, Listen, Repeat technique for approximately 15 minutes a day have most often been assessed and shown gains over two-to-three-week periods, but the pattern of incremental acquisition of items over successive treatment phases is common to both techniques.

Complementing this treatment-monitoring-revision practice approach to treatment delivery is a continual treatment approach, treating the same words over long periods to support maintenance of treatment gains. This removes the need for monitoring to identify words for revision practice, so it is more efficient in terms of treatment preparation time, and more feasible in clinical settings where frequent review is difficult. In studies using continual long term treatment, Participant S5 with nf/avPPA showed stable or better retrieval of treated items after 97 weeks in a treatment study[30], and 4 participants with svPPA showed rapid gains that plateaued and were maintained before gradually declining over 18-24 months' treatment[55]. Participant CT2 with lvPPA carried out home treatment 3 times a week after a 6-week treatment period, and maintained treated items near ceiling for a year, supported by her carer who had been fully trained to administer the treatment[40]. A heterogeneous group of 11 individuals with lvPPA or svPPA treated with phonological and orthographic variants of a Look, Listen, Repeat technique over 6 months showed better written and spoken word retrieval for treated than untreated items after this period[32]. The

long-term treatment studies conducted by Meyer and colleagues include the largest cohorts of individuals in PPA treatment studies (up to 26 participants) and highlight the significant prophylactic benefit of ongoing treatment for items that an individual with PPA is still able to name[32,56].

An important clinical question, then, is whether a potential candidate for lexical retrieval treatment is likely to be able to undertake treatment activities over months-to-years. Answering this question will involve assessment of lexical retrieval and other aspects of lexical knowledge (semantic, phonological, orthography), episodic memory as an indication of the integrity of medial temporal memory structures, and executive function and attentional abilities to establish the individual's potential to organize and engage with treatment activities. It will also be important to consider the individual's motivation to carry out treatment activities. Communication partners have reported the motivation of the individual with PPA to be the factor that most determines adherence to lexical retrieval treatment[57]. Piloting treatment on a small set of items can help to establish an individual's motivation[57]. Two participants in the literature who carried out treatment and maintained upwards of 120 words over the longest time periods[30,54] were noted to be highly motivated and organized in undertaking their treatment activities, supported by normal mood, and relatively preserved executive functioning and episodic memory. If a participant is suited to long-term lexical retrieval treatment, successive sets of items can be introduced over time, allowing an individual to relearn perhaps 40 to 150 communicatively important words, and to maintain currently-known words with prophylactic treatment, with the aim of maintaining a core vocabulary for as long as possible[55]. Items can be withdrawn from and re-introduced to treatment using monitoring and revision practice or can be treated continually.

Generalization of treatment gains to untrained items, tasks and linguistic contexts

A third source of evidence on the relative benefits of different lexical retrieval treatment techniques comes from research on generalization to untreated items, tasks, and linguistic contexts. Generalization to untreated items is rare in the PPA literature as in the stroke aphasia treatment literature[58]. Item generalization has been reported in several lexical retrieval treatment studies since our 2009 review[8,28,31,38,56,59], however the effects are small and in some cases likely to be statistically unreliable. Cueing hierarchy techniques have shown promising item generalization in some studies[9,50] but not others[40,41].

Generalization to untreated tasks (object description and naming to description[34,42], semantic feature verification[60]) has been reported following COEN training with individuals with svPPA. Other individuals with svPPA demonstrated generalization of treatment for partially-known items using a Look, Listen, Read technique[28] to untreated tasks including video description, word-picture matching and – importantly in respect to the benefit of the treatment for everyday life – to actions in response to household requests (e.g. Can you bring me two plates?). At least three studies have also reported *over*generalization of relearning in svPPA, such that participants overextend treated object names (e.g. owl) incorrectly to items they are unable to name (e.g. eagle)[61] or even, sometimes, to items they could name correctly prior to treatment. Such overgeneralization reflects the impoverished semantic representations of the untreated items[53,62]. Individuals with better-preserved semantic knowledge make fewer overgeneralizing errors[53].

A number of studies have reported increased word production (not limited to treated items) in discourse tasks as a generalized benefit of treatment[8,23,29]. At present these results need replication and should be interpreted with caution. They may be confounded by practice effects, with only a single discourse sample acquired before and after treatment, and/or sampling variability, since the amount a person says at a particular

session can be affected by many factors over and above treatment. The most encouraging result from our research group with regard to generalization of treatment benefits to everyday discourse is from Participant S5[63]. She was asked a series of conversation-like questions (e.g. What are you doing in your garden?) in a semi-structured interview repeated over a two year period, for most of which time she was carrying out a Look, Listen, Repeat treatment. At the end of two years, she used more treated than untreated items to answer the questions, and although her use of untreated words declined over this period, her use of treated items remained stable. The benefit of lexical retrieval treatment for supporting conversation was only apparent after a long period of continuous treatment during which her retrieval of untreated words declined precipitously.

The clinical application of research on generalization of lexical retrieval treatment in PPA is that semantically-focussed treatments for svPPA may enrich impoverished semantic representations for treated items, supporting their use in everyday comprehension tasks, but also introducing the possibility of erroneous overgeneralization when semantic memory is sufficiently impaired. Look, Listen, Repeat treatments may benefit comprehension of partially-known items in svPPA. Cueing hierarchies may yield small benefits for untreated items, lexical retrieval in context treatments may promote connected speech and discourse production[8,45,23], and very long term treatment in the context of significant word retrieval decline may support a small number items that can maintain responses in conversational speech[63]. At this point in time, although all these generalization effects merit further investigation, they should be considered much less reliable than immediate gains on treated items, reiterating the priority of treating communicatively important words. A number of researchers offer thoughtful accounts of how to select such words[41,55,64]. Methods included asking individuals with PPA and their communication partners about important conversation topics and particular classes of

items that cause frustration (e.g. names of family members), visiting the home and photographing the person's own items for inclusion in treatment materials, and sampling the person's ability to communicate about personally important topics to identify words for prophylactic treatment or relearning treatment.

Individuals who did not show immediate treatment gains

A final source of information about the relative effectiveness of lexical retrieval treatment techniques in PPA comes from the small number of studies in which individuals who carried out lexical retrieval treatment did *not* show the expected immediate gains. DM, an individual with svPPA, was able to improve lexical retrieval in word generation tasks by practising those tasks, whereas AM, a similar individual noted by the same authors, was not[10]. Graham and colleagues suggested this was due to the greater phonological than semantic emphasis of the tasks carried out by AM compared with DM. Conversely, one individual with nf/avPPA did not benefit from a semantically-focussed technique[65]. In both these studies, treatment may have focussed on retained abilities without sufficiently targeting compromised abilities. In our recent study, Participant S3 with lvPPA and Participant M1 with svPPA did not show immediate gains following a Look, Listen, Repeat treatment[30]. We were unsure as to whether these individuals had not been able to adhere to the home treatment due to additional cognitive and/or psychiatric impairments (anxiety, memory and attentional difficulties in the case of Participant S3 and cognitive inflexibility and obsessive behavior in Participant M1), compounded by a lack of support in carrying out the treatment activities, or whether the individuals had conducted treatment as recommended with genuine null effects. This group of studies highlight the potential importance of language and nonlanguage cognitive processes in treatment response, and the need to establish with a pilot treatment program at the outset of treatment whether an individual is able to make immediate gains.

Non-invasive brain stimulation studies

Although the precise mechanism supporting lexical retrieval and other cognitive functions is unknown, both rTMS and tDCS are thought to increase synaptic activity in the targeted brain network[66,67]. In rTMS, a time-varying magnetic field is generated by running alternating current through a coil applied over the scalp. At high frequencies (above 5 Hz), this induces action potentials in the underlying cortical and white matter neurons, with potentially long-lasting effects on neuronal excitability[68,69]. All five studies that investigated lexical retrieval following rTMS in PPA[13,66,69,70,71] stimulated the left (and in one case, also the right) dorsolateral prefrontal cortex. They reported improvements in tasks including verb production, word generation, paragraph writing and action naming in participants with nf/avPPA, and the effects were relatively short-lived (back to baseline at one week retest in one study and three months in another). One brief abstract reported adverse events and suggested that rTMS might not safe in advanced disease[71].

tDCS is reported to be safer, easier to use, lower in cost, and more portable than rTMS[67]. In tDCS, a small current (1-2 mA) applied to the scalp via two surface electrodes modulates neuronal excitability without directly inducing action potentials[68]. Anodal tDCS, in which the current runs from the positive to the negative electrode, has an excitatory effect which is enhanced when combined with behavioral treatment activities[72]. A range of montages (relative positioning of anodal and cathodal electrodes) combined with a range of behavioral treatments or other language activities have been used. In one study, gains with tDCS accompanied by cyclical standard naming treatment were greater than with treatment alone[61], and were maintained for two months following tDCS[73]. Treatment responses vary across individuals[61,74], and have been associated with differences in grey matter volume in critical language regions[75], consistent with findings in the

behavioral treatment studies that better outcomes are associated with less severe disease[27], and suggesting that intervention early in disease progress might be more successful.

Clinical implications of lexical retrieval treatment research in PPA: A summary

This increasing research on lexical retrieval treatment for individuals with PPA over the last decade continues to provide evidence of immediate treatment gains in most individuals, and maintenance of gains from months-to-years in some individuals with ongoing treatment. The goal of treatment is to restore and maintain retrieval (and in svPPA, comprehension) of a set of core vocabulary items for as long as possible[55,74]. Treatment can be delivered by the clinician face-to-face in the clinic or remotely using the telephone[53,62] or a telemedicine platform[9,5,26,29,46,56], by a trained primary communication partner at home[40,60], or by the individual with PPA working on home treatment tasks, which are the mainstay of long-term treatment. The research has important implications for how we should select and deliver lexical retrieval treatment and whom we should offer it to. This paper concludes with some questions to consider when deciding whether to implement or continue with a behavioral lexical retrieval treatment.

(i) Are there communicatively important words that are retrieved unreliably or not at all that the individual will be motivated to target in treatment, and/or words the person is still able to retrieve that they will be motivated to treat prophylactically?

(ii) What does language and cognitive assessment reveal about the current trajectory of decline of the individual's progressive aphasia, given that gains and maintenance are more likely when the individual has milder disease and carries out treatment over a longer period?

(iii) What does assessment reveal about the trajectory of decline in the individual's semantic, lexical-phonological and orthographic knowledge that indicates residual

strengths? These can guide selection of a treatment technique likely to capitalize on those strengths while targeting areas of weakness.

(iv) Does the individual have relatively preserved episodic memory to support learning in treatment?

(v) What does cognitive assessment reveal about the individual's executive functioning and attention, and, in turn, their likely ability to organize ongoing home treatment activities and engage in them as instructed?

(vi) What does a preliminary (two-to-three week) trial of the planned treatment on a small number of difficult-to-name items suggest about the individual's potential to make immediate gains in treatment, and about their motivation to carry out treatment activities, perhaps over a period of months to years? Conversely, does it raise any "red flags" that treatment could be distressing, including obsession with treatment activities, anger, frustration or anxiety?

(vii) Are there other options among the suite of communication interventions available for people with PPA and their communication partners (see the other papers in this special issue) that would support this individual's communication and psychosocial well-being better than, or in addition to, lexical retrieval treatment?

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Chapter 6
The right word at the right time? General Discussion

This thesis was motivated by the question of whether lexical retrieval treatment supports individuals with PPA in finding the right word at the right time. The first aim was to investigate lexical retrieval treatment outcomes for individuals with PPA carrying out Repetition and Reading in the Presence of a Picture. Chapters 2 and 3 reported a single case series experimental design treatment study conducted with a heterogeneous convenience sample of ten individuals recruited from PPA clinics in Sydney and Germany. The second aim was to develop resources that can be used to support the translation of knowledge about lexical retrieval treatment research in PPA into clinical practice with individuals with PPA. Chapters 4 and 5 offered two such resources. This General Discussion summarises the main contributions of the thesis, and situates the research in this thesis in the context of issues related to (i) the effectiveness of Repetition and Reading in the Presence of a Picture treatment in PPA, (ii) candidacy for lexical retrieval treatment in different PPA variants, (iii) treatment mechanisms in lexical retrieval treatment, and (iv) the integration of lexical retrieval treatment into person- and relational-centred care (Bourgeois, Brush, Douglas, Khayum & Rogalski, 2016; Morhardt & Spira, 2013) for individuals with PPA.

Main contributions of the thesis

The heterogeneous sample of eight individuals reported in Chapter 2 allowed us to observe a range of treatment outcomes and adherence patterns under the same treatment protocol. With some variation in individual patterns across sets of words, retrieval of treated words was generally better at the end of 6 – 22 months' ongoing treatment, relative to the beginning of the study, for three individuals. With similar caveats about individual variation, word retrieval was either stable or had declined, relative to the beginning of the study, without ongoing treatment for four other individuals. Two of these four individuals did not make treatment gains, an outcome that is rarely reported. There was little evidence for generalisation to untreated words.

Because the best outcomes were achieved by the individuals who maintained treatment for the longest periods, we also described the factors characterising those who did and did not continue with long term treatment. The individual with nf/avPPAwho adhered to treatment over the longest period in Chapter 2 demonstrated preserved insight into her language impairments and was motivated to conduct home treatment. Her episodic and semantic memory, picture naming and executive functioning were within normal limits on formal testing. She had levels of depression and anxiety within normal levels, and excellent social support and speech language pathology support. Three individuals were unable to continue with the study due to declining health. Two others did not adhere to treatment: one was 18 years post-onset of symptoms and began demonstrating obsessive behaviour. The other was impaired on a range of language and cognitive tests on pretreatment neuropsychological assessment, and support from a family member that assisted her in accessing treatment actvities was withdrawn during the course of the study.

Chapter 3 reported two further individuals who undertook the same treatment for a two-week period, and who also demonstrated immediate treatment effects for treated items, no generalisation to retrieval of untreated items in picture naming, and decline without ongoing treatment. For these individuals, the gains on treated items did not generalise to a semi-structured interview designed to elicit conversation-like speech under standardised conditions. Both participants withdrew from this study to travel overseas, then recommenced treatment activities upon their respective returns, but in both cases declining health led to subsequent discontinuation of treatment.

Chapter 4 described a hypothetical clinical scenario in which the manager of a speech pathology service who has received a referral for a man with nonfluent/agrammatic variant PPA asks whether there is evidence for speech, language and communication interventions in PPA. The article follows recommendations for evidence-based practice to guide clinicians through the formulation of an answerable clinical question, a literature review, and a critical appraisal of a research report, leading to the development of a clinical bottom line about suitability of lexical retrieval treatment in this hypothetical case.

Chapter 5 (supported by Appendix I) reviewed the research on lexical retrieval treatment in PPA from the earliest reports to the end of January 2018. It grouped the reported behavioural treatments into five general techniques (“standard” naming treatment, Look, Listen, Repeat (described elsewhere in this thesis as Repetition and Reading in the Presence of a Picture) treatment, cueing hierarchies, semantically-focused treatments, and

lexical retrieval in context. The chapter considered whether there was evidence that any of the behavioural techniques might be more effective than others, reaching several conclusions. First, treatments that appeared to utilise an individual's residual lexical and cognitive strengths were likely to be associated with the best outcomes. Second, Look, Listen, Repeat techniques and cueing hierarchies were associated with incremental retrieval of additional items over successive treatment phases, and with prophylactic support for items the individual could still retrieve at the start of the study. This supports a long-term approach to treatment in which new items can be gradually added, and then treated using a monitoring-and-revision-practice approach, or treated continually, over an extended period. Third, generalisation to untreated *items* was rarely reported, with the clinical implication that treatment items should be important to the individual with PPA. Generalisation to untreated *tasks* has been demonstrated in several svPPA treatment studies using Look, Listen, Repeat to treat words for which individuals with svPPA retain partial semantic knowledge, or using semantically-focused techniques to partially reinstate semantic knowledge. Performance on these tasks suggests that comprehension as well as lexical retrieval can be supported in svPPA. Results demonstrating generalisation to connected speech/discourse/interview are preliminary and need further support. Finally, the small number of individuals who have been reported not to show a treatment effect, together with an emerging understanding of the importance of long term adherence to treatment, suggest that treatment should be piloted for a short period before introducing treatment for the long term. This would indicate whether a candidate for lexical retrieval treatment appears motivated to undertake ongoing treatment, and does not have any adverse responses that would counter-indicate lexical retrieval treatment.

Repetition and Reading in the Presence of a Picture Treatment in PPA

The studies in Chapters 2 and 3 investigated Repetition and Reading in the Presence of a Picture treatment because it could be self-administered by the participants in the study at home. This allowed near-daily treatment that could be maintained over a long period, by comparison with the service delivery constraints that apply when treatment needs to be administered by a clinician. Repetition and Reading in the Presence of a Picture treatment was also hypothesised to provide multimodal activation of the lexical network for treated items. This was thought to improve lexical retrieval of treated items by increasing the activation of the phonological form, and to prophylactically support activation of less compromised regions of the lexical/speech production work.

The research in Chapters 2 and 3 does not speak to the question of how Repetition and Reading in the Presence of a Picture treatment compares with other techniques. Variants of this treatment have been compared within and between a small number of participants in Single Case Experimental Design studies (Savage, Ballard, Piguet & Hodges, 2013, Savage, Piguet & Hodges, 2014, 2015; Meyer, Getz, Brennan, Hu & Friedman, 2016; Meyer, Snider, Eckmann & Friedman, 2015) and across groups (Meyer, Faria, Tippett, Hillis & Friedman, 2017; Meyer, Tippett & Friedman, 2016; Meyer, Tippett, Turner & Friedman, 2018), see Chapter 5. Chapter 5 also discussed how the outcomes in Chapters 2 and 3 of this thesis compared with outcomes using the Lexical Retrieval Cascade cueing hierarchy. A more systematic comparison of immediate gains, maintenance with ongoing treatment, and generalisation to untreated items and tasks across treatments awaits future study. This could be undertaken in experimental investigations of treatment mechanisms as discussed further below. It would also be informative to more closely interrogate the results of existing studies, including an evaluation of risk of bias and an aggregation of results across comparable existing studies of sufficient quality. The review in Chapter 5 presents the first exploration of issues to arise from a review of lexical retrieval treatment studies in PPA that is planned for the future. Beales et al., in press, evaluates many studies of lexical retrieval in PPA using the RoBiNT criteria (Tate et al.) and opens a discussion about the treatment mechanisms in play.

This thesis investigated generalisation of Repetition and Reading in the Presence of a Picture treatment to a structured interview for two individuals in Chapter 3. Although there have been anecdotal reports of generalisation to everyday communicative situations (Hameister, Nickels, Abel & Croot, 2017; Heredia, Sage, Lambon Ralph, Berthier, 2009), there was no evidence that improved retrieval of treated words in picture naming for these two individuals generalised to retrieval of those words in the interview in Chapter 3. This null effect may indicate a genuine lack of generalisation from a less to a more ecologically valid task, or it may reflect the difficulty of observing such an effect due to the difficulty of reliably sampling everyday language use in everyday contexts (Webster, Whitworth & Morris, 2015). The individuals in Chapter 3 treated 30 items for two weeks, with minimal change in their language and cognitive profiles over this period. By contrast, Participant S5/ANT (Chapter 2/Appendix 2) treated 128 items for 90 weeks, and her use of these items in the interview remained stable after the long treatment period. Even in this study (Appendix II), generalisation of treatment to conversation-like speech in the interview was

not easy to demonstrate, because the variability in quantity of Participant S5/ANT's output over different sessions in the interview meant the decline of untreated words was statistically marginal. It will be critical to further investigate the benefits of lexical retrieval treatment to support conversation, in well-designed, well-powered longitudinal studies to establish the potential (or not) of lexical retrieval treatment to support everyday communication. Treating lexical retrieval in context might be a promising avenue to explore, first because the preliminary results provide some support for generalisation to discourse (Greenwood, Grassly, Hickin & Best; 2010; Whitworth), second, because the treatment tasks more closely approximate everyday situations and can integrate supports for lexical retrieval in those situations such as retrieval cues and strategies, and third, because the treatment would need to take into account the additional demands of spoken language production in connected speech and conversation (Dipper, Black & Bryan, 2005).

Candidacy for lexical retrieval treatment in different PPA variants

The research questions about efficacy of lexical retrieval treatment addressed in this thesis were initially driven by the frustration people with PPA experience from word-finding difficulty, that our research team has observed over many years, and that has been reported in the literature. A number of published accounts of frustration at word-finding difficulty report people with nf/avPPA (e.g. Nickels & Croot, 2009; Rohrer, et al., 2008; Rutherford, 2009). Although some authors have suggested that word-finding is "not typically a primary concern in individuals with nf/avPPA" (Rising, 2014, p. 140), that claim is not consistent with these accounts.

In Chapter 2, Participant S5 (Participant ANT in Appendix II), also an individual with nf/avPPA, reported and demonstrated frustration with word-finding difficulties, and was highly motivated to carry out lexical retrieval therapy activities. Her adherence to treatment and her outcomes over a two-year period (Chapter 2, Appendix II) suggest that a promising candidate for lexical retrieval treatment in nf/avPPA might have well-preserved cognitive function, accompanied by good motivation, positive mood, social support and speech pathologist support. Conversely, lexical retrieval was not a suitable long-term option for Participant S1 in Chapter 2. Although she presented with similar characteristics to Participant S5, the disease progressed rapidly, and communication support, dysphagia management, and palliative care became the clinical priorities. Another two individuals with nf/avPPA, Participant S4 with a progressive supranuclear palsy syndrome in Chapter

2 and CSN with a corticobasal syndrome in Chapter 3, were longer post-onset of PPA symptoms, and experienced less benefit than Participant S5, consistent with the claim also made elsewhere in this thesis that a range of disease and participant factors contribute to treatment outcomes.

Individuals with svPPA may also experience concern and frustration at vocabulary loss in the early stages of the disease. These individuals can also make excellent gains at the single word level, for example, Participant VC reported by Suarez-Gonzalez, Savage, & Caine (2016) who re-learned 158 words in separate phases of standard naming treatment and COnceptual ENrichment treatment, and the individual reported by Evans, Quimby, Dickey, & Dickerson (2016) who relearned 139 words using elements of standard naming treatment with semantically-focused treatment with more frequent treatment of harder-to-name items. Participants with svPPA can also be highly motivated and self-initiate treatment, for example DM, reported by Graham, Patterson, Pratt & Hodges (1999) developed his own word relearning program, and the individual reported by Evans et al. (2016) developed a communication notebook. They may also maintain treatment over long periods (see Evans et al., 2016 and Reilly, 2016, for individuals who continued treatment for 20 and 24 months; respectively). The potential for lexical retrieval treatment to bolster item-specific representations in semantic memory (Suarez Gonzalez et al. 2015, 2016) and thereby support everyday comprehension (Savage et al., 2014), as well as word retrieval, warrants ongoing application of, and investigation of, lexical retrieval treatment with individuals with svPPA.

The individuals with semantic dementia reported in Chapter 2 were not able to adhere to treatment over a six-month period, however, for several reasons as noted earlier, including being many years post-onset of symptoms, co-morbid obsessive behaviour, comorbid cognitive decline, and lack of support in accessing treatment activities. We suggest that the candidate most likely to benefit from treatment would, instead, be similar to the woman reported by Evans and colleagues (2016), who had good cognitive functioning, language abilities (apart from word comprehension and picture naming) within normal limits on an aphasia battery, and sufficient executive function and motivation to devise her own compensatory strategies and manage treatment with flashcard software over 20 months. A caveat with regard to suitability of lexical retrieval treatment in svPPA is related to the incorrect overgeneralisation of treated item names to other objects and concepts reported in several studies (Hoffman, Clark, Jones & Noonan, 2015; Mayberry, Sage, Ehsan, & Lambon Ralph, 2011). Retrieving a semantic associate

of a difficult-to-retrieve word may facilitate communication in the same way circumlocution does, but it may lead to confusion in other instances, and need speech pathologist support.

The empirical work in the present thesis offers some evidence to support lexical retrieval treatment in lvPPA, with modest immediate treatment gains by one individual with lvPPA (DQI, Chapter 3), but not by the others (Participants S3 and M2, Chapter 2). Further, although generalisation to untreated items has been reported for a relatively high proportion of the individuals with lvPPA in published lexical retrieval treatment studies, this study did not support that finding. It is likely that mild disease, relatively preserved language and non-language cognition and positive mood support lexical retrieval treatment gains in lvPPA as in nf/avPPA and svPPA, whereas none of the three participants in Chapters 2 and 3 showed these characteristics. One was 5 years post-onset of symptoms, and the other two, who were 2.5 and 2 years post-onset, had a number of cognitive impairments additional to language (reduced score on a cognitive screen, reduced spatial attention and episodic memory), as well as at least moderate depression on a self-report scale. Participant CT2 with lvPPA (Grasso et al) offers a contrast to Participants DQI, S3, and M2 in this study, and represents characteristics that indicate good candidacy for treatment. Participant CT2 was 66 years of age, 3 years post-onset of symptoms and 1 year post-diagnosis with PPA, with otherwise minimal non-language cognitive impairment, and semantic memory just below the normal range. She maintained gains from an initial 6 weeks of treatment using Lexical Retrieval Cascade treatment (a cueing hierarchy which also incorporates retrieval practice) over a further 12 months of treatment administered by her partner at home. Cognitive abilities remained stable on testing over the period of the study. Participant CT2 was able to provide more informative and efficient semantic information during circumlocution, used self-cueing to aid retrieval of untreated words in conversation, and was less frustrated and more confident in talking with familiar and unfamiliar people, as a result of treatment.

Treatment mechanisms in lexical retrieval treatment

The current thesis investigated the same treatment across a heterogeneous sample, and considered two mechanisms that might have accounted for treatment gains across variants and individuals. The first of these mechanisms was the complementary learning systems account of new learning (Chapter 2), the most-frequently invoked account of lexical retrieval gains in svPPA (e.g. Savage et al., 2013; Suarez-Gonzalez et al., 2015;

Hoffman et al., 2015), first proposed by Graham et al. (1999). Under this account, gains are dependent on a medial temporal memory system that learns new material but is unable to consolidate it to cortical regions due to loss of neuronal function as a consequence of disease (Graham et al., 1999). Most learning of a newly-presented set of items occurs very soon after the items enter treatment (e.g. Henry et al., 2013) and does not appear to increase with longer treatment (Chapter 2; also Savage et al., 2013), suggesting that information is written quickly to this system. Learning must then be continually refreshed to maintain information in the medial temporal system in the absence of consolidation to cortical memory stores, although better treatment gains and maintenance in milder disease is attributed to partial availability of these cortical stores, albeit compromised (Savage et al., 2013; 2014).

The second mechanism discussed was long-term repetition priming (Chapter 2), an account borrowed from the stroke aphasia literature, according to which the target of treatment is the activation of the phonological form. It was, however, also noted in this account that treatment success is likely to depend on the pattern of preserved and impaired language abilities of the individual with PPA (Chapter 5), which in turn depends on the integrity of diverse brain regions that support language (e.g. Jarso et al., 2013). For example, compromised activation of the phonological form might be supported by relatively preserved orthographic processing (Krajenbrink, Croot, Taylor0Rubin & Nickels, under review). Future studies would therefore benefit from the traditional cognitive neuropsychological approach in which a model-driven analysis of preserved and impaired language and cognitive function is used to inform the treatment technique. This is particularly important in experimental treatment for PPA presentations that do not fit the consensus variants, for example, spelling treatment for an individual whose dysgraphia was prominent in the clinical presentation (Rapp & Glucroft, 2009). In the context of the interactions between linguistic, cognitive, participant and treatment factors observed in the current research (Chapter 5), single case experimental design treatment studies continue to have a place in providing communication support for individuals that can also inform theory about these interactions (Nickels, Rapp & Kohnen, 2015).

Rising (2014) also notes that the causes of lexical retrieval impairment may differ with PPA variant. This suggests we should also be asking whether there are treatment mechanisms specific to each variant, a question not investigated in this thesis. For example, in semantic variant PPA, a number of studies have attempted to rebuild or bolster the individual's disintegrating semantic networks for treated items. Graham and

colleagues (1999) suggested that insufficient semantic focus might have accounted for AM's failure to benefit from a word retrieval therapy. In nf/avPPA, the primary deficits are post-semantic, and must arise in accessing or selecting phonological and/or motor representations for production. In at least one case (Flannagan, Copland, van Hees, Byrne & Angwin, 2016), a semantically-focused treatment was ineffective for an individual with nf/avPPA. There is a caveat on future investigation of variant-specific treatments, also drawn from a cognitive neuropsychological approach. Because the variants are syndrome labels that do not reliably capture the pattern of impaired and preserved language and cognitive processes at an individual level, we will be able more reliably to interpret treatment outcomes when the individual profile and individual treatment response are also reported in a case series design, as used in this thesis.

Other learning and memory processes apart from those described in the complementary learning systems account have also been a focus of investigation in PPA treatment. Massed practice to improve learning is one pillar of Constraint-Induced Aphasia Therapy (Hameister et al., 2017). Meyer and colleagues (e.g. Meyer et al., 2018) asked participants to recognise the stimuli they were shown in a variant of a Look, Listen, Repeat technique to ensure they were paying attention during encoding. Hoffman et al. (2015) investigated the effects of variability in presentation order and exemplars to test a hypothesis derived from classical learning theory that this would lead to greater recall. Henry and colleagues (e.g. Henry et al., 2013) included retrieval practice to augment a cueing hierarchy, and Bier et al., (2009) implemented spaced retrieval to capitalise on implicit learning mechanisms. A range of authors have investigated errorless learning (e.g. Jokel & Anderson, 2012), and lexical retrieval in context approaches (Whitworth et al., 2018), attempting to provide context during treatment that will assist with retrieval in real-world tasks. All these mechanisms require further investigation.

Further investigation of treatment factors in lexical retrieval outcomes must occur in theoretically-motivated experimental tests of potential treatment mechanisms (Beales et al., in press). Information about regional brain structure prior to treatment, and about functional changes associated with treatment outcomes in PPA (Beeson et al., 2011; Dressel et al., 2010; Jokel et al., 2016; Marcotte & Ansaldo, 2010; Meyer et al., 2017) is also contributing to an understanding of treatment mechanisms at the level of brain structure and function. Analyses at the level of brain structure and function are also likely to assist in predicting which individuals with PPA are most likely to benefit from lexical retrieval treatment in future (Hillis, 2018; Tsapkini, 2017).

An understanding of treatment mechanisms at the cognitive-linguistic and brain structure/function levels of analysis is all the more important given the relatively recent development of transcranial direct current stimulation (tDCS) as an experimental treatment after brain injury. tDCS is typically administered concurrently with behavioural treatment activities, and is thought to enhance the functioning of the language/cognitive network engaged by those activities. tDCS combined with behavioural treatment is beginning to show promise in PPA, delivering treatment effects above those associated with the same behavioural treatment in the absence of tDCS (Tsapkini, 2017; Tsapkini et al., 2014; see also Chapter 5). If tDCS augments behavioural treatment effects, it makes sense to optimise behavioural treatment effects through a systematic account of the mechanisms responsible for them. An understanding of the roles of various brain regions will assist in formulating hypotheses about the optimal tDCS montages for diffferent disease presentations and language treatments.

Person- and relational-centred care for individuals with PPA

To the extent that the clinical evidence supporting lexical retrieval treatment in PPA is robust, we need to further consider how lexical retrieval treatment can be included into a model of person-centred/relational-centred care for people with PPA. There is growing evidence for a range of impairment-directed and activity-participation-directed interventions for individuals with PPA, and indications that brain stimulation combined with behavioural treatment shows promise. The advice from McNeil and Duffy (2001) quoted at the beginning of this thesis remains current, that we should select from among the available evidence-based approaches those that are consistent with the individual's needs and the clinician's philosophy of care. Chapter 4 offered a model for investigating the evidence on a specific clinical question about PPA treatment, and Chapter 5 proposed some questions to guide clinical decision-making about implementing or continuing with behavioural lexical retrieval treatment.

The WHO International Classification of Functioning, Disability and Health (WHO, 2002) provides a framework that describes how interventions to support people with PPA can be targeted at the impairment, the person's activities and life participation, the person and their environment (Chapter 1). Interventions should be based on a comprehensive assessment that includes an understanding of the goals of the individual with PPA and their close others (Volkmer, 2013). In the absence of disease-modifying treatments, alongside lexical retrieval and other impairment-directed treatments, a range of

activity-/participation-directed interventions are available that may include education, emotional and social support, communication training, and coping strategies, provided to the person with PPA, their close others and their wider communication networks. Various types of AAC may support communication within these networks, ranging from communication boards, cards, smartphones and text to speech devices to aid in the communication of specific messages, through photographs and mementos (e.g. bus tickets, grocery bills, concert programmes) that can support narratives about activities and people, to personal objects, pets and music that can support relational interconnectedness (Bourgeois et al., 2016; Brandt, Gordon & Quimby, 2016; Fried-Oken, Mooney & Peters, 2015; Mooney, Beale & Fried-Oken, in press). Interventions to promote communication can in turn support the relationships, identity, autonomy, and instrumental ADLs of individuals with PPA and their close others, within person- and relational-centred approaches (Kindell et al., 2015; Morhardt & Spira, 2013). These approaches encourage people interacting with individuals with dementia to remember their fundamental personhood beyond their symptoms and disease: their sensations, emotional responses, remaining strengths, and positive functions, and their interdependence and interconnectedness with their close others (Morhardt & Spira, 2013). The choice of intervention would typically change with disease progression, and interventions may be introduced proactively in anticipation of future decline (Rogers, King & Alarcon, 2000).

There is an important recent initiative in which individuals living with dementia (including Alzheimer-type, vascular, Lewy body and other dementia syndromes as well as PPA) have begun to ask that researchers take account of their priorities and views, as summarised in the phrase, “nothing about us without us” (e.g. Dementia Alliance International, 2018). It should be an ongoing goal to incorporate the views of individuals with PPA and their close others into research on clinical management of PPA, including research on lexical retrieval treatment.

Concluding Remarks

The research on lexical retrieval treatment in PPA presented in this thesis indicates that there is typically an immediate treatment effect for treated items, and that individuals who adhere to treatment over months to years may be able to maintain initial gains for long periods. This means their retrieval of treated items may be stable or better after a period of treatment than at the beginning of treatment, which is no small achievement in the context of neurodegenerative disease where untreated items may be declining,

sometimes precipitously. Items that can be retrieved at the start of the treatment may be treated prophylactically, while items that could not be retrieved at the start of treatment may be restored. This thesis also argued that individual outcomes depend on complex interactions between disease factors, cognitive and language processing factors, personal and environmental factors. These interactions are not yet well understood, but they suggest there is unlikely to be a "one size fits all" treatment (Henry, Beeson & Rapcsak, 2008).

Lexical retrieval treatment will be clinically most appropriate in PPA when we treat the "right" words with the "right" individual with PPA, at the "right" time in the disease course. To further understand the interplay between disease, participant, and treatment factors, and their effect on treatment outcomes, it remains critical to select well-formulated research questions to constrain future treatment studies (Rochon, Simic, & Seixas Lima, 2016). There are theoretically important questions to answer about the impaired lexical retrieval mechanisms specific to particular individuals and to each PPA variant, and as well as about the role of language, memory, other cognitive processes and brain regions and functions involved in lexical retrieval: these answers will contribute to optimising treatment gains. There are clinically important questions to answer about whether outcomes in lexical retrieval treatment are clinically significant, and where lexical retrieval treatment fits in a comprehensive mangement pathway for individuals with PPA, not least in the perspective of individuals with PPA and their close others.

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Webster, J., Whitworth, A., & Morris, J. (2015). Is it time to stop "fishing"? A review of generalisation following aphasia intervention. *Aphasiology*, *29*(11), 1240-1264. doi: 10.1080/02687038.2015.1027169

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Appendix I

Literature search for review in Chapter 5

The review reported in Chapter 5 was based on a literature search conducted by the author as described below.

Eligibility criteria

We reviewed studies of individuals diagnosed with semantic-nonfluent/agrammatic- or logopenic-variant PPA or with other presentations of PPA that did not meet consensus criteria (Gorno Tempini et al., 2011) for the former three variants. Studies needed to report one or more interventions designed to remediate lexical retrieval impairments, that is to improve retrieval of high information words in written or spoken form, conducted as Single Case Experimental Design (SCED) studies or group studies. Studies needed to report immediate treatment outcomes, with reporting of maintenance and generalisation measures optional. The search was conducted from 1982 until end of January 2018, commencing in 1982 as the report by Mesulam (1982) is often taken as the first report of PPA in the modern era. We restricted the search to reports published in English in peer-reviewed journals.

Information sources

Studies were identified by searching the following electronic databases: Allied and Complementary Medicine Database (AMED; 1985 to February 2018), Cochrane Database of Systematic Reviews (CDSR; 2005 to 31 January 2018), Embase (1974 to 7 February 2018), Pre-Medline, Medline (1946 to January week 5 2018), PsycINFO (1967-January Week 5 2018) using the Ovid platform, as well as Speechbite. We also identified earlier reviews (Beales et al., in press; Croot, Nickels, Laurence & Manning, 2009; Jokel, Graham, Rochon & Leonard, 2014; Casarin, Branco, Pereira, Kochhann, Gindri & Fonesca, 2014) including two systematic reviews (Carthery-Goulart et al., 2013; Cadorio, Lousada, Martins, & Figueiredo, 2017) on this or related topics and hand-searched these for additional references. Results were limited to journal articles that were published in English and peer reviewed. The search was performed from 1 to 3 February 2018.

Search

We used the following search terms to search all Ovid databases: fronto-temporal dementia, fronto-temporal lobar degeneration, Alzheimer$, PSP, progressive supranuclear palsy, CBD, cortico-basal degeneration, Pick$ disease, progressive aphasi$, progressive anomi$, progressive language impair$, progressive non-fluent aphasi$, progressive

logopenic aphasi$, progressive mixed aphasi$, PPA, semantic dementia, lexical retrieval, word retrieval, word-finding, word recall, semantic, anomi$, naming, training, retraining, learning, relearning, intervention$, therap$, rehabilitation, treatmen$. See Table 1 for the full search strategy used in Ovid databases. In Speechbite, a smaller, bespoke database for treatment interventions across the scope of speech pathology practice, we searched for all records using the search terms "primary progressive aphasia", and for all records using "semantic dementia."

Study selection

A total of 800 articles were retrieved using the search strategy described above. Duplicates were removed, and the remaining articles were screened and included or excluded as illustrated in the flow diagram in Figure 1. Studies included as per the flow diagram are the studies illustrated by year in Figure 1, Chapter 5.

Data items

We extracted the number of participants with each PPA variant from each study, as summarised in Table 2.

Table 1.

Search strategy used in the Ovid databases.

Database(s): **AMED (Allied and Complementary Medicine)** 1985 to January 2018, **Books@Ovid** January 29, 2018, **EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to January 25, 2018, **Embase** 1974 to 2018 January 30, **Ovid MEDLINE(R)** 1946 to January Week 3 2018, **PREMEDLINE (Most Recently Published)**, **PsycINFO** 1967 to January Week 4 2018

Search Strategy:

#	Searches	Results
1	(fronto-temporal dementia or fronto-temporal lobar degeneration or FTD).mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	11361
2	Alzheimer$.mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	396691
3	(PSP or progressive supranuclear palsy).mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	21906
4	(CBD or cortico-basal degeneration).mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	17994
5	Pick$ disease.mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	10246
6	1 or 2 or 3 or 4 or 5	445711
7	(progressive aphasi$ or progressive anomi$ or progressive language impair$).mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	4634
8	progressive non-fluent aphasi$.mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	562
9	progressive logopenic aphasi$.mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	19
10	progressive mixed aphasi$.mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	3
11	PPA.mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	8812
12	semantic dementia.mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	4916
13	7 or 8 or 9 or 10 or 11 or 12	15752
14	6 or 13	456727
15	(lexical retrieval or lexical).mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	44689
16	(word or word retrieval or word finding or word-finding or word recall).mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	198503
17	(semantic or anomi$ or naming).mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	139544
18	15 or 16 or 17	316598
19	(training or retraining or re-training).mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	1157461
20	(learning or relearning or re-learning).mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	1110743
21	(interventio$ or therap$ or rehabilitation or treatmen$).mp. [mp=ab, hw, ti, tx, bt, kw, ct, tn, ot, dm, mf, dv, fx, nm, kf, px, rx, ui, sy, tc, id, tm]	19811435
22	19 or 20 or 21	21286040
23	((lexical retrieval or lexical or (word or word retrieval or word finding or word-finding or word recall) or (semantic or anomi$ or naming)) adj3 (training or retraining or re-training or (learning or relearning or re-learning) or (interventio$ or therap$ or rehabilitation or treatmen$))).mp.	11771
24	14 and 23	857
25	limit 24 to human [Limit not valid in AMED,Books@Ovid,CDSR; records were retained]	807
26	limit 25 to yr="1982 -Current"	807
27	remove duplicates from 26	496

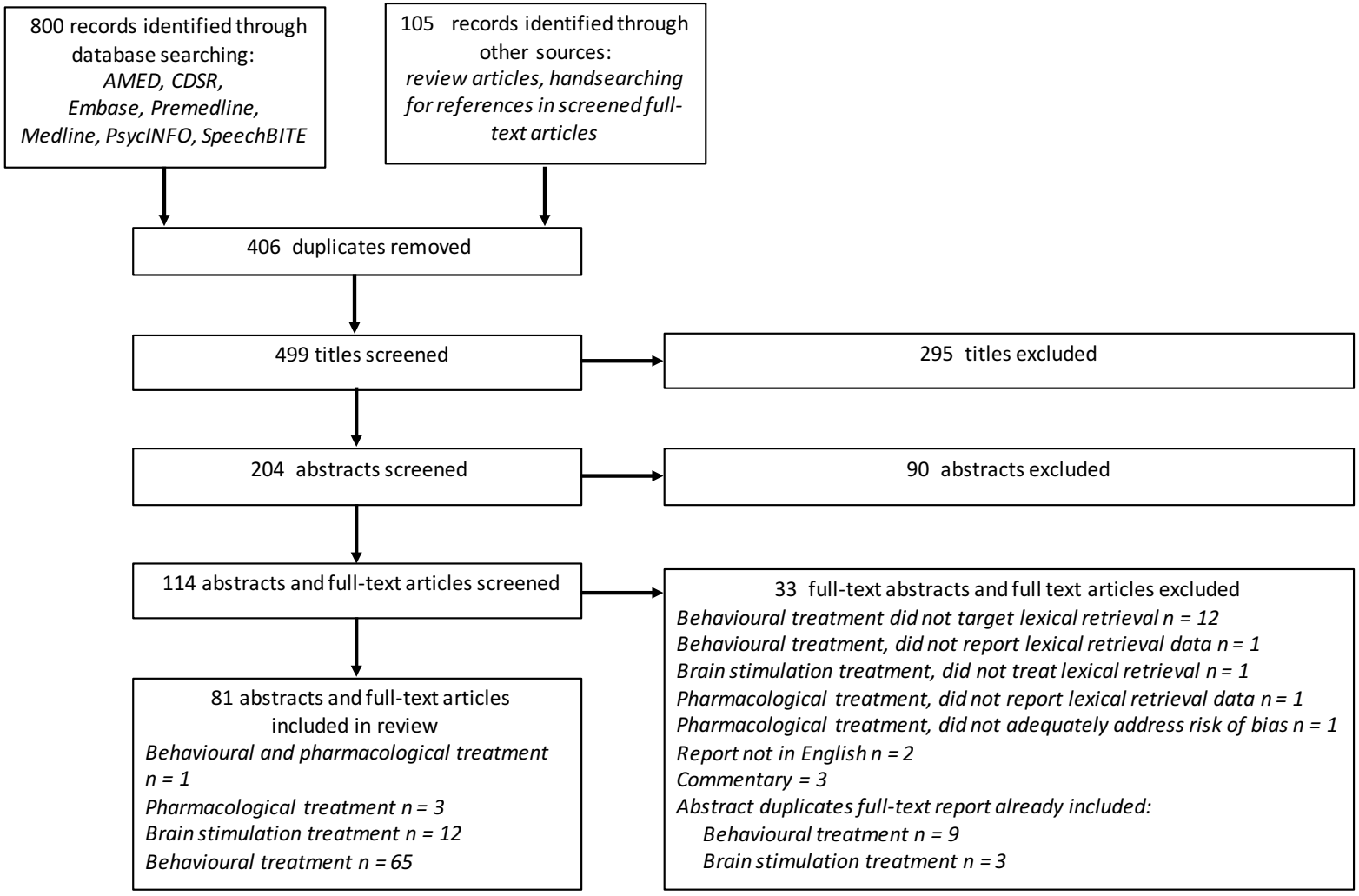

Figure 1. Number of studies identified, screened, excluded and included at each stage of the literature search.

Table 2.

Summary of participant counts by PPA presentation.

References by treatment type	PPA variant				
	sv	**nf/av**	**lv**	**m**	**NOS**
Behavioural & pharmacological treatment					
McNeil, M. R., Small, S. L., Masterson, R. J., & Fossett, T. R. D. (1995). Behavioral and pharmacological treatment of lexical semantic deficits in a single patient with primary progressive aphasia. American Journal of Speech-Language Pathology, 4, 76–87. doi:10.1044/1058-0360.0404.76					1
Total	**0**	**0**	**0**	**0**	**1**
Pharmacological treatment					
Reed, D. A., Johnson, N. A., Thompson, C., Weintraub, S., & Mesulam, M.-M. (2004). A clinical trial of Bromocriptine for treatment of primary progressive aphasia. Annals of Neurology, 56, 750–750. doi:10.1002/ana.20301					6
Kowa, H., Seki, T., Yamamoto, M., Kanda, F., & Toda, T. (2012). Treatment of primary progressive aphasia with Rivastigmine. Annals of Neurology, 72, S45–S46.	1	5			
Decker, D. A., & Heilman, K. M. (2008). Steroid treatment of primary progressive aphasia. Archives of Neurology, 65, 1533–1535. doi:10.1001/archneur.65.11.1533		1			
Total	**1**	**6**	**0**	**0**	**6**
Brain stimulation					
Cotelli, M., Manenti, R., Petesi, M.,Brambilla, M.,Cosseddu, M., Zanetti, O., Miniussi, C., Padovani, A., Borroni, B. (2012) Using transcranial direct current stimulation (tDCS) to treat agrammatic variant of primary progressive aphasia. Poster presented at the International Conference on Frontotemporal Dementia, Manchester, England.	*				
Cotelli M. et al. (2016) Grey matter density predicts the improvement of naming abilities after tDCS intervention in agrammatic variant of primary progressive aphasia. Brain Topography, 29, 738-51		8			
Gervits F, Ash S, Coslett HB, Rascovsky K, Grossman M, Hamilton R. (2016) Transcranial direct current stimulation for the treatment of primary progressive aphasia: An open-label pilot study. *Brain & Language, 162*, 35-41		6			
Hung, J., Bauer, A., Grossman, M., Hamilton, R. H., Coslett, H. B., & Reilly J. (2017). Semantic feature training in combination with transcranial direct current stimulation (tDCS) for progressive anomia. *Frontiers in Human Neuroscience, 11*, 253.	2		1		
Roncero, C., Kniefel, H., Thiel, A., Probst, S., & Chertkow, H. (2017). Inferior parietal transcranial direct current stimulation with training improves cognition in anomic Alzheimer's disease and frontotemporal dementia. *Alzheimers and Dementia, 3*, 247-53. doi: 10.1016/j.trci.2017.03.003	2	6	2		
Chertkow H, Roncero C, Kneifel H, et al. (2017) Transcranial direct current stimulation (tDCS) improves picture naming in Alzheimer Disease and Frontotemporal dementia.(P3. 089). Neurology, 88(16 Supplement):P3-089					2
Wang, J., Wu, D., Chen, Y., Yuan, Y., & Zhang, M. (2013).		1			

Effects of transcranial direct current stimulation on language improvement and cortical activation in nonfluent variant primary progressive aphasia. *Neuroscience letters*, *549*, 29-33.					
Bereau, M., Magnin, E., Nicolier, M., Berthet, L., Dariel, E., Ferreira, S., ... & Vandel, P. (2016). Left prefrontal repetitive transcranial magnetic stimulation in a logopenic variant of primary progressive aphasia: a case report. *European Neurology*, *76*(1-2), 12-18.			1		
Carrai, R., et al. (2013) rTMS in the Primary Progressive Aphasia: Two case-reports taken from open study treatment protocol. Clinical Neurophysiology, 124, e189-e223. doi:10.1016/j.clinph.2013.06.164		2			
Cotelli M, et al. (2012) Prefrontal cortex rTMS enhances action naming in progressive non-fluent aphasia. European Journal of Neurology, 19, 1404-1412.		10			
Finocchiaro, C., Maimone, M., Brighina, F., Piccoli, T., Giglia, G., & Fierro, B. (2006). A case study of primary progressive aphasia: Improvement on verbs after rTMS treatment. Neurocase, 12, 317–321. doi:10.1080/13554790601126203					1
Trebbastoni, A., Raccah, R., deLena, C., Zangen, A., & Inghilleri, M. (2013). Repetitive deep transcranial magnetic stimulation improves verbal fluency and written language in a patient with primary progressive aphasia-logopenic variant (LPPA). Brain Stimulation, 6, 545–553. doi:10.1016/ j.brs.2012.09.014	1				
Total	**4**	**33**	**5**	**0**	**1**
Behavioural treatment					
Beales, A., Cartwright, J., Whitworth, A., & Panegyres, P. K. (2016). Exploring generalisation processes following lexical retrieval intervention in primary progressive aphasia. *International journal of speech-language pathology*, *18*(3), 299-314. doi: 10.3109/17549507.2016.1151936	3		1		
Beeson, P. M., King, R. M., Bonakdarpour, B., Henry, M. L., Cho, H., & Rapcsak, S. Z. (2011). Positive effects of language treatment for the logopenic variant of primary progressive aphasia. Journal of Molecular Neuroscience, 45, 724–736. doi:10.1007/s12031-011-9579-2			1		
Bier, N., Brambati, S., Macoir, J., Paquette, G., Schmitz, X., Belleville, S., ... & Joubert, S. (2015). Relying on procedural memory to enhance independence in daily living activities: smartphone use in a case of semantic dementia. *Neuropsychological rehabilitation*, *25*(6), 913-935.	1				
Bier, N., Macoir, J., Gagnon, L., Van der Linden, M., Louveaux, S., & Desrosiers, J. (2009). Known, lost, and recovered: Efficacy of formal-semantic therapy and spaced retrieval method in a case of semantic dementia. Aphasiology, 23, 210–235. doi:10.1080/00207590801942906	1				
Croot, K., Taylor, C., Abel, S., Jones, K., Krein, L., Hameister, I., ... & Nickels, L. (2015). Measuring gains in connected speech following treatment for word retrieval: A study with two participants with primary progressive aphasia. *Aphasiology*, *29*(11), 1265-1288. doi: 10.1080/02687038.2014.975181		1	1		
Croot, K., Raiser, T., Taylor-Rubin, C., Ruggero, L., Ackl, N., Wlasich, E., Stenglein-Krapf, G., Rominger, A., Danek, A.,	2	3	2	1	

Scharfenberg, A., Foxe, D., Hodges, J.R., Piguet, O., Kochan, N.A., & Nickels, L. (under review). Lexical retrieval treatment in primary progressive aphasia: An investigation of treatment duration in a heterogeneous case series. *Cortex*. [Chapter 2 of this thesis]					
D'Honincthun, P, Gambazza, CC, Clarke, S. (2017) Restoration of both conceptual knowledge and word form retrieval in a case of semantic dementia in two compared treatments. *Stem-, Spraak- en Taalpathologie*. *22*(Suppl. 2), 98-99.	1				
Dewar, B. K., Patterson, K., Wilson, B. A., & Graham, K. S. (2009). Re-acquisition of person knowledge in semantic memory disorders. *Neuropsychological Rehabilitation*, *19*(3), 383-421.	1				
Dressel, K., Huber, W., Frings, L., Kümmerer, D., Saur, D., Mader, I., … Abel, S. (2010). Model-oriented naming therapy in semantic dementia: A single-case fMRI study. Aphasiology, 24, 1537–1558. doi:10.1080/02687038.2010.500567	1				
Evans, W. S., Quimby M., Dickey M. W., & Dickerson B. C. (2016). Relearning and Retaining Personally-Relevant Words using Computer-Based Flashcard Software in Primary Progressive Aphasia. *Frontiers in Human Neuroscience, 10*, 561, 1-8.	1				
Farrajota, L., Maruta, C., Maroco, J., Martins, I., Guerreiro, M., & de Mendonça, A. (2012). Speech therapy in primary progressive aphasia: A pilot study. Dementia and Geriatric Cognitive Disorders Extra, 2, 321–331. doi:10.1159/000341602	2	2	6		
Flanagan, K.J., Copland, D.A., van Hees, S., Byrne, G.J., & Angwin, A.J. (2016) Semantic feature training for the treatment of anomia in Alzheimer disease: A preliminary investigation. *Cognitive and Behavioural Neurology, 29*(01), 32–43.		1			
Frattali, C. (2004). An errorless learning approach to treating dysnomia in frontotemporal dementia. Journal of Medical Speech-Language Pathology, 12, XI–XXIV. Retrieved from http://go.galegroup.com/ps/i.do?id=GALE%7CA123086160&v=2.1&u=utoronto_main&it=r&p=AONE&sw=w&asid=c1345991df41e8ca2cc855bdf342a1db					1
Funnell, E. (1995). A case of forgotten knowledge. In R. Campbell & M. A. Conway (Eds.), *Broken memories: Case studies in memory impairment* (pp. 225–236). Oxford, UK: Blackwell.	1				
Graham, K. S., Patterson, K., Pratt, K. H., & Hodges, J. R. (1999). Relearning and subsequent forgetting of semantic category exemplars in a case of semantic dementia. Neuropsychology, 13, 359–380. doi:10.1037/0894-4105.13.3.359	1				
Graham, K. S., Patterson, K., Pratt, K. H., & Hodges, J. R. (2001). Can repeated exposure to "forgotten" vocabulary help alleviate word-finding difficulties in semantic dementia? An illustrative case study. Neuropsychological Rehabilitation, 11, 429–454. doi:10.1080/09602010042000060	*				
Grasso, S. M., Shuster, K. M., & Henry, M. L. (2017).				1	

Comparing the effects of clinician and caregiver-administered lexical retrieval training for progressive anomia. *Neuropsychological Rehabilitation*. Advance online publication. doi: 10.1080/09602011.2017.1339358.					
Hameister, I., Nickels, L., Abel, S., & Croot, K. (2017). "Do you have mowing the lawn?"–improvements in word retrieval and grammar following constraint-induced language therapy in primary progressive aphasia. *Aphasiology*, *31*(3), 308-331. doi: 10.1080/02687038.2016.1197558		2			
Henry, M. L., Rising, K., DeMarco, A. T., Miller, B. L., Gorno-Tempini, M. L., & Beeson, P. M. (2013). Examining the value of lexical retrieval treatment in primary progressive aphasia: Two positive cases. *Brain and Language*, *127*(2), 145-156. doi: 10.1016/j.bandl.2013.05.018	1		1		
Henry, M. L., Beeson, P. M., & Rapcsak, S. Z. (2009). Treatment for lexical retrieval in progressive aphasia. Aphasiology, 22, 826–838. doi:10.1080/02687030701820055	1	1			
Heredia, C.G., Sage, K., Lambon Ralph, M. A., & Berthier, M. (2009). Relearning and retention of verbal labels in a case of semantic dementia. Aphasiology, 1–18. doi:10.1080/02687030801942999	1				
Hoffman, P., Clarke, N., Jones, R. W., Noonan, K. A. (2015). Vocabulary relearning in semantic dementia: Positive and negative consequences of increasing variability in the learning experience. *Neuropsychologia, 76*, 240-25. doi: 10.1016/j.neuropsychologia.2015.01.015	3				
Jokel, R., Rochon, E. A., & Leonard, C. (2002). Therapy for anomia in semantic dementia. Brain and Cognition, 49, 241–244. doi:10.1006/brcg.2001.1477	1				
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Total	**93**	**29**	**32**	**2**	**27**

KEY: PPA = primary progressive aphasia, sv = semantic variant, nf/av = nonfluent/agrammatic variant, lv = logopenic variant, m = mixed presentation, NOS = not otherwise specified, * = when no count is given for a study, it is presumed the participants are included in another report by the same group. Similarly some participant counts are lower than reported for the study, where it has been assumed some of the participants' data have been reported previously by the same group.

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Appendix II

POSTER:

Croot, K., Taylor-Rubin, C., Ruggero, L., A., Scharfenberg, A., Foxe, D., Hodges, J.R., Piguet, O., & Nickels, L. (2017, November) Long-term word retrieval treatment gains in nonfluent-agrammatic variant primary progressive aphasia. Poster presented at the *ARC Centre for Cognition and its Disorders Annual Workshop*, Hunter Valley, Australia.

Notes:

This poster is Reference No. 63 in the article presented in Chapter 5.

Participant ANT reported in the poster is Participant S5 in the article under review in Chapter 2.

Long-term word retrieval treatment gains in nonfluent-agrammatic variant primary progressive aphasia: A single case study

Karen Croot[1,2,3] | Cathleen Taylor Rubin [1,2,4] | Leanne Ruggero[1,2,3] | Angela Scharfenberg[5] | David Foxe[5] | John R. Hodges[5,6,7]
Olivier Piguet[3,5,7] | Lyndsey Nickels[1,2]

1 | ARC Centre of Excellence in Cognition and its Disorders, Macquarie University, Sydney, Australia 2 | Department of Cognitive Science, Macquarie University, Sydney, Australia 3 | School of Psychology, The University of Sydney, Australia 4 | Speech Pathology Department, War Memorial Hospital, Sydney, Australia 5 | Brain and Mind Centre, The University of Sydney, Australia 6 | Central Clinical School, The University of Sydney, Australia 7 | ARC Centre of Excellence in Cognition and its Disorders, The University of Sydney, Australia

Background

- **Nonfluent/agrammatic primary progressive aphasia (nf/aPPA)** is a dementia syndrome characterised by effortful spoken language production including word-finding difficulty
- Approximately 30 published studies of word retrieval treatment in all clinical variants of PPA show gains in picture-naming but not generalisation to word retrieval in conversation

AIM: To investigate effects of word retrieval treatment on a conversational task in a person with nf/aPPA

Method

Participant: ANT, 75 years, female, retired executive teacher

- 1 year post-onset nf/aPPA at start of study, excellent non-language cognitive function, mood, motivation to participate
- Neuropsychological assessments over period of study showed further decline in word production and declining executive function, while visuospatial function, comportment and self-care remained relatively intact

Treatment:

- Repetition and Reading in the Presence of a Picture
- Used home computer, 5 days per week, estimated 10-30 mins per day, long-term
- 118 personally relevant lexical items associated with preferred conversation topics

Image credit: iStock.com/RUSSELLTATEdotCOM

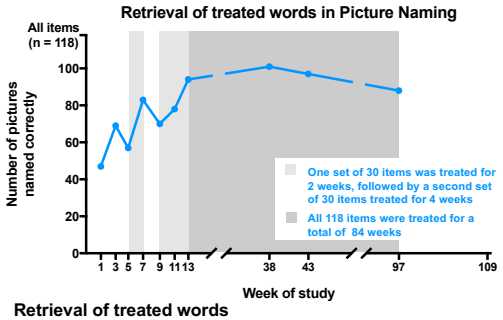
Semi-structured interview

- Repeated sampling of ANT's conversation about her interests and activities using similar questions in a similar order
- Counted number of treated versus untreated content items at each time point. Examples below show more **treated** than **untreated** items used in Week 109, not seen in Week 1

Week 1:
Researcher 1: Would you mind telling me about things you like to do outside the house?
ANT: Um, um um **gardening**. Um **Round up** the the **weeds**. I have **four daffodils**.
Researcher 1: What are your other favourite plants?
ANT: Um, **camellias** and **roses**.
Researcher 1: How many different sort of roses would you have?
ANT: **Queen Queen Elizabeth, Prince, Princess Elizabeth, Merrymakers roses**, **white**. I think it's **eight** er **roses**.

Week 109:
Researcher 2: So what are you doing in your garden?
ANT: **Camellias** and **hydrangeas** and **weeding** yes
Researcher 2: I've heard you have a lot of roses? How many different sorts?
ANT: **Sixteen**

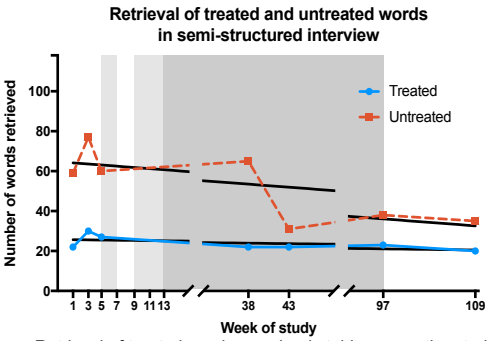
Results: Picture naming



Retrieval of treated words

- Did not decline over 84 week-period in which all items were treated (t_{117} = -1.03, p = 0.847)
- Better at the end of treatment than at the start (t_{117} = 5.45, p < 0.001)

Results: Semi-structured interview



- Retrieval of treated words remained stable across the study period (β = -2.5 ± 1.4, p = 0.143) but retrieval of untreated words declined (β = -15 ± 5.9, p = 0.051)

Conclusions

- **First study to demonstrate such long-term benefits of word retrieval treatment in picture naming in nf/aPPA**
- **Provisional experimental evidence that treatment can generalise to word retrieval in conversation in PPA**
- **ANT's good cognitive function, mood and motivation may have contributed to her positive treatment outcomes**

Appendix III

Author contribution statements for article presented in Chapter 2

Croot, K., Raiser, T., Taylor-Rubin, C., Ruggero, L., Ackl, N., Wlasich, E., Danek, A., Scharfenberg, A., Foxe, D., Hodges, J.R., Piguet, O., Kochan, N.A., & Nickels, L. (under review). Lexical retrieval treatment in primary progressive aphasia: An investigation of treatment duration in a heterogeneous case series.

Original signed statements by all co-authors are on record at Macquarie University.

Author Contribution Statement for Paper Contributed to Thesis by Publication, Macquarie University

Candidate Name: Karen Croot
Degree title: Doctor of Psychology (Clinical Neuropsychology)

Paper title: Lexical retrieval treatment in primary progressive aphasia: An investigation of treatment duration in a heterogeneous case series

As an author of the above paper contributed to a thesis by publication, I declare that I have made the contributions described below.

Name **Signature** **Date**

AUTHOR LIST AND CONTRIBUTIONS:

Karen Croot
Conceptualization of study, design of study methods, supervision of study, acquisition of treatment study data, analysis and interpretation of data, drafting of original and revised manuscripts

Theresa Raiser
Design of study methods, supervision of study, participant recruitment, acquisition of background clinical data and treatment study data, contribution to analysis and interpretation of data, revision of the manuscript for intellectual content

Cathleen Taylor-Rubin
Conceptualization of study, design of study methods, supervision of study, participant recruitment, acquisition of background clinical data and treatment study data, revision of the manuscript for intellectual content

Leanne Ruggero
Design of study methods, acquisition of treatment study data, revision of manuscript for intellectual content

Nibal Ackl
Acquisition of background clinical data, revision of the manuscript for intellectual content

Elisabeth Wlasich
Participant recruitment, acquisition of background clinical data, revision of the manuscript for intellectual content

Adrian Danek
Supervision of the study, participant recruitment, acquisition of background clinical data, revision of the manuscript for intellectual content

Angela Scharfenberg
Acquisition of background clinical data, revision of the manuscript for intellectual content

David Foxe
Acquisition of background clinical data, revision of the manuscript for intellectual content

John R. Hodges
Acquisition of background clinical data, revision of the manuscript for intellectual content

Olivier Piguet
Acquisition of background clinical data, revision of the manuscript for intellectual content

Nicole A. Kochan
Acquisition of background clinical data, revision of the manuscript for intellectual content

Lyndsey Nickels
Conceptualization of study, design of study methods, data coding and matching treatment Sets A and B in Sydney data, supervision of study, contribution to analysis and interpretation of data, drafting of revised manuscript

Appendix IV

Author contribution statements for article presented in Chapter 3

Croot, K., Taylor, C., Abel, S., Jones, K., Krein, L., Hameister, I., Ruggero, L. & Nickels, L. (2015) Measuring gains in connected speech following treatment for word retrieval: A study with two participants with primary progressive aphasia. *Aphasiology*, 29(11), 1265-1288. DOI: 10.1080/02687038.2014.975181

Original signed statements by all co-authors are on record at Macquarie University.

Author Contribution Statement for Paper Contributed to Thesis by Publication, Macquarie University

Candidate Name: Karen Croot
Degree title: Doctor of Psychology (Clinical Neuropsychology)

Paper publication details:

Croot, K., Taylor, C., Abel, S., Jones, K., Krein, L., Hameister, I., Ruggero, L. & Nickels, L. (2015) Measuring gains in connected speech following treatment for word retrieval: A study with two participants with primary progressive aphasia. *Aphasiology*, 29(11), 1265-1288. DOI: 10.1080/02687038.2014.975181

As an author of the above paper contributed to a thesis by publication, I declare that I have made the contributions described below.

Name **Signature** **Date**

AUTHOR LIST AND CONTRIBUTIONS:

Karen Croot
Conceptualization of study, design of study methods, supervision of study, acquisition of treatment study data, contribution to analysis of lexical retrieval data, interpretation of data, descriptive analysis of structured interview data, co-drafting of original manuscript, figures and tables, drafting of revised manuscript.

Cathleen Taylor
Conceptualization of study, design of study methods, supervision of study, participant recruitment, acquisition of background clinical data and treatment study data, revision of manuscript for intellectual content.

Steffi Abel
Contribution to study methods, acquisition of treatment study data, contribution to preliminary analysis of data, revision of manuscript for intellectual content.

Kelly Jones
Acquisition of treatment study data, contribution to semi-structured interview coding methods and coding.

Luisa Krein
Contribution to semi-structured interview coding methods and coding.

Inga Hameister
Contribution to semi-structured interview coding methods and coding.

Leanne Ruggero
Contribution to study methods, acquisition of treatment study data, revision of manuscript for intellectual content.

Lyndsey Nickels Conceptualization of study, design of study methods, supervision of study, data coding and matching of treatment sets, statistical analysis of lexical retrieval data, interpretation of data, co-drafting of original manuscript, contribution to drafting of revised manuscript.

Appendix V

Author contribution statements for article presented in Chapter 4

Croot, K., Taylor, C & Nickels, L (2011) What's the evidence? Evidence for speech, language and communication interventions for progressive aphasia. *ACQuiring Knowledge in Speech, Language and Communication*, *13*(1), 38-41.

Original signed statements by all co-authors are on record at Macquarie University.

Author Contribution Statement for Paper Contributed to Thesis by Publication, Macquarie University

Candidate Name: Karen Croot
Degree title: Doctor of Psychology (Clinical Neuropsychology)

Paper published as: Croot, K., Taylor, C & Nickels, L (2011) Evidence for speech, language and communication interventions in progressive aphasia. *ACQuring Knowledge in Speech, Language and Hearing, 13*(1), 37-40.

As an author of the above paper contributed to a thesis by publication, I declare that I have made the contributions described below.

Name **Signature** **Date**

AUTHOR LIST AND CONTRIBUTIONS:

Karen Croot
Invited by journal editorial committee to write article, conceptualization of manuscript according to journal guidelines, literature search and critical appraisal or articles according to journal guidelines, drafting of original and revised manuscripts.

Cathleen Taylor-Rubin
Conceptualization of manuscript according to journal guidelines, developed clinical scenario, revision of the manuscript for intellectual content.

Lyndsey Nickels
Conceptualization of manuscript according to journal guidelines, revision of the manuscript for intellectual content.

Appendix VI

Copy of final ethics approval letters from

- Human Research Ethics Committee - South Eastern Sydney Illawarra Northern Hospital Network
- Human Research Ethics Committee – Macquarie University

SOUTH EASTERN SYDNEY
ILLAWARRA
NSW HEALTH

HUMAN RESEARCH ETHICS COMMITTEE – Northern Hospital Network

Room G71, East Wing
Edmund Blacket Bldg
Prince of Wales Hospital
Cnr High & Avoca Streets
RANDWICK NSW 2031
Tel: (02) 9382 3587
Fax: (02) 9382 2813

15 March 2011

Dr Karen Croot
Room 443 Brennan MacCallum Building
School of Psychology A18
University of Sydney
NSW 2006

Dear Dr Croot

HREC ref no: 11/017
Project title: The right word at the right time: keeping communication going in progressive aphasia.

Thank you for submitting the above project for ethical and scientific review. The project was first considered by the Human Research Ethics Committee (HREC) at its meeting held on 22 February 2011.

At that meeting the Committee requested that the investigator provide further information/clarification or modification and resubmit an amended Participant Information Statement and Consent Forms. The Committee delegated final approval to the Executive Officer.

I am pleased to advise that with your correspondence dated 14 March 2011, the requested information and revised documents were received incorporating the recommendations of the Committee. Ethical approval has been granted for the above project to be conducted at the War Memorial Hospital.

The following documentation has been approved:

- NEAF (NHMRC version)
- Protocol, version 1, dated 28 January 2011
- Advertisement, version 1, dated 28 January 2011
- Information Sheet and Consent Form – person with progressive aphasia, version 2, dated 14 March 2011
- Spouse/carer/guardian Information Sheet and Consent Form – person with progressive aphasia, version 2, dated 14 March 2011

Conditions of approval

1. This approval is valid for 5 years from the date of this letter.
2. Annual reports must be provided on the anniversary of approval.
3. A final report must be provided at the completion of the project.

A

4. Proposed changes to the research protocol, conduct of the research, or length of approval will be provided to the Committee.
5. The Principal Investigator will immediately report matters which might warrant review of ethical approval, including unforeseen events which might affect the ethical acceptability of the project and any complaints made by study participants.

Optional It is the responsibility of the sponsor or the principal (or co-ordinating) investigator of the project to register this study on a publicly available online registry (eg Australian New Zealand Clinical Trials Registry www.anzctr.org.au).

For NSW Public Health sites only: You are reminded that this letter constitutes ethical approval only. You must not commence this research project until you have submitted your Site Specific Assessment to the Research Governance Officer of the appropriate institution and have received a letter of authorisation from the General Manager or Chief Executive of that institution.

Should you have any queries, please contact the Research Support Office on (02) 9382 3587. The HREC Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Research Support Office website: http://www.sesiahs.health.nsw.gov.au/Research_Support/NHN/.

Please quote **HREC ref no: 11/017** in all correspondence.

We wish you every success in your research.

Yours sincerely

Deborah Adrian

Deborah Adrian
Executive Officer
Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)*, NHMRC and Universities Australia *Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

Lyndsey Nickels
<lyndsey.nickels@mq.edu.au>

ethics application

1 message

Fran Thorp <Frances.Thorp@vc.mq.edu.au> 27 July 2007 at 15:32
Reply-To: Frances.Thorp@vc.mq.edu.au
To: lnickels@maccs.mq.edu.au

Dear Lyndsey

Re: Using language impairment to inform theories of language processing (HE27JUL2007-R05342)

The above application was reviewed by the Ethics Review Committee (Human Research). Approval of the above application is granted, subject to your compliance with the conditions listed below.

Research on the project may not proceed until a written response to these items has been reviewed and approved and you have received formal correspondence from the Committee confirming Final Approval for this project.

The conditions of approval are as follows:

1. Please clarify the following points regarding the recruitment of participants;
(a) Item 5.1 states that there will be a small sample size. Can you please provide an indication of what numbers are planned for both control and test participants.

(b) Given that a large number of researchers are involved, a pro forma letter or email would seem to be required to ensure uniformity of approach in recruiting participants. Please provide a copy of this item.

(c) Given the sensitivity of the subject, please comment on whether the telephone is an appropriate method for recruitment. If it is then perhaps again, it would be advisable to have a pro forma on hand to assist the contact person with their recruitment call.

(d) Please comment on the informality of the advertisement which, although suitable for use within the University, may be rather confronting for general use in newspapers.

(e) Have you considered that, unless patients with cognitive problems are specifically excluded there will be some participants whose carers or next of kin will have to give permission? Please comment on this issue.

2. Item 3.1. In the unlikely event that a participant becomes extremely distressed, at what stage will the interviews be terminated?

3. At Item 6.6 it is stated that feedback is given. Will this be oral or written feedback?

4. Item 10.1 mentions stimuli may be used. Since the funding support (Item 1.8) is for a Fellowship, not for research project(s) per se, this specific information has not been supplied. Please provide information on the types of stimuli that are planned.

Please forward your response to in writing either to the address below or via email to ethics.secretariat@vc.mq.edu.au. Once you have met all the conditions of approval you will be sent a Final Approval letter.
Please do not hesitate to contact me if you wish to discuss any of the above issues.

Kind regards
Fran

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