Treatment dose in post-stroke aphasia: a systematic scoping review

Sam R. Harvey, MSpPath [a,b], Marcella Carragher, PhD [a,b], Michael Walsh Dickey, PhD [b,c,d], John E. Pierce, BSpPath [a,b], and Miranda L. Rose, PhD [a,b]

[a]*School of Allied Health, Human Services and Sport, La Trobe University, Melbourne, Australia;* [b]*Centre of Research Excellence in Aphasia Recovery and Rehabilitation, Australia;* [c]*Geriatric Research Education and Clinical Center, VA Pittsburgh Healthcare System, USA;* [d]*University of Pittsburgh, USA*

Sam R. Harvey. Health Sciences 1, La Trobe University, Plenty Road, Bundoora 3083, Australia. ORCID identifier: 0000-0002-4839-2117 Twitter: @SRHarvey_ sam.harvey@latrobe.edu.au

Marcella Carragher. Health Sciences 1, La Trobe University, Plenty Road, Bundoora 3083, Australia. ORCID identifier: 0000-0002-7200-6968 Twitter: @MarcellaC_SP marcella.carragher@latrobe.edu.au

Michael Walsh Dickey. 6077 Forbes Tower, University of Pittsburgh, Pittsburgh PA 15260, USA. ORCID identifier: 0000-0002-9068-3313 mdickey@pitt.edu

John E. Pierce. 2-6 Hopetoun Street, Elsternwick 3185, Australia. ORCID identifier: 0000-0001-5164-5106 Twitter: @johnpierce85 pierce.john.e@gmail.com

Miranda L. Rose. Health Sciences 1, La Trobe University, Plenty Road, Bundoora 3083, Australia. ORCID identifier: 0000-0002-8892-0965 Twitter: @rose_mirandaros M.rose@latrobe.edu.au

Corresponding author:

Professor Miranda Rose, PhD

Discipline of Speech Pathology
School of Allied Health, Human Services and Sport
College of Science, Health and Engineering
La Trobe University
Bundoora 3086 AUSTRALIA
T: +61 3 9479 2088
E: m.rose@latrobe.edu.au

Conflicts of interest

The authors declare no potential conflict of interest.

Funding

This work was supported by an Australian Government Research Training Program Scholarship and the NHMRC funded Centre for Research Excellence in Aphasia Recovery and Rehabilitation (#1153236).

ABSTRACT

Little is known about how the amount of treatment a person with aphasia receives impacts aphasia recovery following stroke, yet this information is vital to ensure effective treatments are delivered efficiently. Furthermore, there is no standard dose terminology in the stroke rehabilitation or aphasia literature. This scoping review aims to systematically map the evidence regarding dose in treatments for post-stroke aphasia and to explore how treatment dose is conceptualised, measured and reported in the literature. A comprehensive search was undertaken in June, 2019. 112 intervention studies were reviewed. Treatment dose (amount of treatment) has been conceptualised as both a measure of time and a count of discrete

therapeutic elements. Doses ranged from one to 100 hours, while some studies reported session doses of up to 420 therapeutic inputs per session. Studies employ a wide variety of treatment schedules (i.e., session dose, session frequency, and intervention duration) and the interaction of dose parameters may impact the dose-response relationship. High dose interventions delivered over short periods may improve treatment efficiency while maintaining efficacy. Person- and treatment-level factors that mediate tolerance of high dose interventions require further investigation. Systematic exploration of dose-response relationships in post-stroke aphasia treatment is required.

Word count: 5,884 (including abstract, tables headings, figure captions, and citations; excluding abbreviation list, bibliography, figure legend, and appendices)

Keywords: Aphasia; stroke; treatment; rehabilitation; dose; scoping review

Abbreviations

CIAT	Constraint-Induced Aphasia Therapy
ICAP	Intensive Comprehensive Aphasia Program
ICF	International Classification of Functioning, Disability, and Health
M-MAT	Multi-Modality Aphasia Therapy
NHMRC	National Health and Medical Research Council
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR	PRISMA Extension for Scoping Reviews
RCT	Randomised Controlled Trial
SCED	Single-case experimental design
SFA	Semantic Feature Analysis
TIDieR	Template for Intervention Description and Replication

Aphasia is a significant acquired language impairment affecting 30% of stroke survivors.[1] Recovery is highly variable and difficult to predict with aphasia persisting as a chronic condition in up to 50% of cases.[2-4] Aphasia is associated with a 2-fold increased risk of mortality,[5] higher healthcare costs,[6] negative consequences for personal relationships, social integration, and economic independence,[3, 7] and is associated with poorer quality of life than many other debilitating health conditions including Alzheimer's disease and cancer.[8] Treatments are needed to reduce the impact of aphasia.

Aphasia treatments may aim to remediate symptoms of language processing impairment (e.g., anomia, agrammatism) by targeting specific linguistic functions (e.g., word retrieval, syntactic processing).[9] Alternatively, intervention may aim to improve how a person communicates with others using pragmatic, functional communication, and social interaction approaches.[9] Results of meta-analyses demonstrate the effectiveness of interventions targeting language impairment, communication activity and participation, and communication-related wellbeing.[10-13] However, little is known about how the amount of treatment a person with aphasia receives impacts aphasia recovery following stroke. This knowledge is vital to improve healthcare efficiency and quality of life for people living with aphasia.

Quantifying aphasia interventions

Defining dose

There is no consensus definition within the stroke rehabilitation literature to describe the amount of treatment a person receives, nor has standard terminology been established in the aphasia literature.[14, 15] Attempts to investigate "dose articulation" within pre-clinical and clinical stroke rehabilitation studies are underway.[16] In the aphasia domain, the terms *dose*, *dosage*, and *intensity* are commonly used interchangeably to refer to divergent concepts; for

example, the number of repetitions within a specific therapy task, the duration and number of sessions, the overall duration of a treatment program, the total number of treatment hours provided over the course of an intervention, or the effort required to successfully complete a task.[14, 15, 17] The lack of consensus definitions and inconsistent use of these terms confounds attempts to examine the individual contribution of each parameter to overall treatment effectiveness.[17]

A way forward

The taxonomy proposed by Warren, Fey, and Yoder[18] and elaborated by Baker[14] provides one definition and delineation of dose and intensity parameters for behavioural interventions (Figure 1). This model is gaining traction in the aphasia treatment literature,[17, 19, 20] but is not yet widely accepted.

The key assertion of this taxonomy is that the amount of therapy provided or received is a product of the number of times the active ingredients of a particular treatment are applied over the course of the treatment schedule. Active ingredients are "the procedures presumed by the interventionists to teach or enhance new learning and behaviour".[18] Closer examination of the quality and quantity of active ingredients may ultimately enhance our understanding of the mechanisms of action that transform received therapy into improved health and wellbeing.[21] Once identified, maximising delivery of active ingredients has the potential to increase treatment efficiency and effectiveness.

Figure 1 Model of dose and intensity parameters involved in determining optimal intervention intensity[14] (reproduced with permission)

Definitions used in this review

In the absence of consensus definitions but informed by the above taxonomy, the following definitions have been adopted for this review:

Therapeutic element	The basic unit of therapy; either a therapeutic input or a client act
Session dose	A quantitative measure of the therapeutic content provided in a session, in minutes or therapeutic elements
Total dose	The number or quantity of doses provided or received over an intervention period e.g., total hours, total number of therapeutic elements

We note that the term 'intensity' has commonly been used to refer to *session frequency.*[14, 18] While treatment intensity is not the focus of this review, it is acknowledged that it is often not possible to discuss dose without reference to intensity.[22] Further, Warren and colleagues and Baker use *cumulative intervention intensity* for what we will refer to as *total dose*.[14, 18]

Measuring dose

Given the lack of consensus definitions, it is unsurprising that a standard basic unit of dose in aphasia interventions has yet to be established. The prevailing convention in aphasia research and clinical practice has been to measure total dose in number of hours or sessions provided or received[12, 23]. Hours of therapy is a convenient measure; it is easy to capture, calculate, and compare from one study to the next, has clinical relevance to service providers, is easily

understood by consumers and health policy makers, and satisfies minimum reporting standards (e.g., TIDieR Item 8[24]).

However, measuring the amount of aphasia intervention in hours is inadequate because of the inherent assumption that all hours of therapy are equal. In standard care, intervention often targets several language and communication goals concurrently. Different goals may require different treatment approaches. Ultimately, one hour of treatment may comprise a variety of different tasks.[25] Furthermore, one study found that direct therapeutic input accounted for only 57% of the intervention session.[26] Unless treatment details are clearly reported and monitored, it is difficult to draw conclusions regarding how often different elements of therapy are being provided. Similarly, the rise of Intensive Comprehensive Aphasia Programs (ICAPs) sees delivery of multifaceted interventions where treatment targets and approaches purposively vary from session to session.[27] Measuring the total dose of complex interventions, such as ICAPs, in hours makes it impossible to examine responses to specific therapeutic elements.

Optimal dose

Determining the optimal amount of treatment is an important component of stroke rehabilitation planning and provision.[28] The term *optimal* conveys aspects of both efficacy and efficiency; the notion of maximal improvement in the minimal amount of time within the constraints of the clinical environment, while meeting patient and clinician expectations of recovery. Currently, clinicians have very little empirical guidance regarding optimal therapy dose across the breadth of communication disorders.[29]

Within the realm of aphasia, evidence suggests there is a range of doses that will result in positive treatment effects. In 2003, Bhogal and colleagues synthesized the existing evidence to investigate the impact of aphasia treatment intensity on recovery of language and

175 communication functions; studies that demonstrated a statistically significant positive
176 treatment effect provided a total of 98.4 hours of therapy or more, whereas ineffective studies
177 provided a total of 43.6 hours of therapy or less.[23] Although based on few studies, many of
178 which confound intensity and dose parameters, this finding lead to the assumption that "more
179 is better" and has heavily influenced the ongoing examination of dose-response relationships
180 in aphasia research. Several meta-analyses have also demonstrated larger treatment effects
181 with greater amounts of therapy.[12, 13] The current clinical reality, however, is that few people
182 will receive 100 hours of intervention due to many factors intrinsic and extrinsic to the
183 treatment recipient.

184 Treatments provided at lower doses (i.e., fewer hours) have been developed and are
185 efficacious. For example, treatment efficacy has been demonstrated after 30 hours of multi-
186 modality aphasia therapy (M-MAT),[30] constraint-induced aphasia therapy (CIAT),[31] and
187 ICAPs[32] where intervention can be provided in either a massed or distributed treatment
188 schedule.[19]

189 The reality is that different therapy targets may require different amounts of treatment
190 delivered at different rates to optimise recovery.[17] For example, optimal gains in naming
191 accuracy may be achieved with a smaller dose of naming treatment as compared to optimal
192 gains in discourse-level auditory comprehension following conversational therapy. At a
193 theoretical level, picture naming in anomia involves stimulation of a relatively simple
194 psycholinguistic process which maps lexical representations to phonological forms involving
195 a relatively discrete neurological network, whereas auditory comprehension in discourse is a
196 far more complex cognitive-linguistic task involving large swathes of both cerebral
197 hemispheres.[33] Furthermore, individual variation in post-stroke aphasia recovery underlines
198 the importance of careful attention to person-level factors that may predict treatment

response.[34] Determining optimal treatment dose for an individual person with aphasia therefore depends on many person- and treatment-level factors.

In summary, treatment effectiveness has been demonstrated over a range of doses which raises a number of important questions. Are lower-dose interventions sufficient or should we expect a greater magnitude of improvement with increased dose of these interventions? Given the literature reported above, at which dose between 30 and 100 hours of a given intervention should we expect optimal recovery for a given individual? What person-level and treatment-level factors are likely to mediate dose-response in aphasia interventions? The answers to these questions will depend on the nature of the relationship between efficacy and dose and, potentially, between efficacy and each independent dose parameter (i.e., session dose, session frequency, and intervention duration).

To improve aphasia recovery we need to understand, investigate, and optimise the therapeutic mechanisms that are driving the brain and behavioural change.[35] Ultimately, there is a pressing need to find more efficient delivery models to allow rapid recovery to acceptable levels for individuals with aphasia. Treatment dose is an important factor that requires immediate systematic investigation.

AIMS

A systematic scoping review was conducted in order to systematically map the evidence regarding treatment dose in post-stroke aphasia and to explore how dose is conceptualised, measured and reported in the aphasia intervention literature.

METHODS

Design

The scoping methodology described by Arksey and O'Malley was adopted as it enables mapping of key concepts underpinning an emerging research area and allows clarification of working definitions and conceptual boundaries of the topic.[36] Additional considerations were drawn from a number of sources to enhance methodological rigour.[37, 38] The PRISMA-ScR checklist was referenced to ensure comprehensive and systematic reporting of the review.[39]

Identifying the research question

Two questions drive this review:

1) In the post-stroke aphasia literature, how is treatment dose conceptualised, measured and reported?
2) Is there sufficient evidence in the post-stroke aphasia treatment literature to conduct meta-analysis on the effect of differing doses on treatment outcomes?

Identifying relevant studies

A comprehensive and systematic search was undertaken in June, 2019 for peer-reviewed randomised controlled trials, quasi-experimental studies, single-case experimental design studies, and case studies which report measures of quantity of behavioural aphasia therapy and aim to investigate the effect of that intervention on language impairment and communication activity/participation for adults with aphasia following stroke.

Using the Preferred Reporting Items for Systematic reviews and Meta-Analysis Guidelines (PRISMA),[40] the following databases were searched, with no language or date limits set: PubMed, Medline, EMBASE, CINAHL, PsycINFO, and Cochrane Library. Table 1 shows search terms relating to post-stroke aphasia, intervention, and dose identified from

relevant literature. These search domains were combined using the AND operator, and the terms within each domain combined using OR. Search terms were modified in line with individual database subject headings. An example of the final search strategy is provided in Appendix 3. Reference lists of included studies were examined to identify additional studies not captured during the systematic search.

Table 1 Search terms relating to treatment dose in aphasia

Selecting studies

Figure 2 shows a PRISMA flow diagram detailing the results of study identification, screening, eligibility, and inclusion. The search yield was imported into citation software and duplicates removed using software and manual checking. Titles and abstracts were then screened by the first author as per the inclusion criteria to determine eligibility for full text review. Twenty percent of full texts were double-screened by a second reviewer (author J. P.) for inclusion, achieving 95% agreement between reviewers. Inconsistencies were discussed and resolved, and inclusion criteria refined to improve application of inclusion/exclusion criteria.

Figure 2 PRISMA flow diagram showing the study selection process

Eligibility criteria

Studies inclusion criteria:

- Full text peer-reviewed journal article in English
- Includes adults presenting with aphasia, at any time after stroke

- Reports primary data from behavioural treatment(s) targeting language impairment or communication activity/participation
- Measures and reports the amount of treatment provided

Charting the data

Where available, data were extracted from each study regarding study characteristics, participant characteristics, intervention details, and dose parameters (Table 2). A second author (J.P.) double-rated 10% of studies for study design and outcome measure, reaching 91% consistency. A data charting template was created and populated by the first author. The template was modified iteratively to accommodate additional concepts as these were encountered in the literature.

Table 2 Data items extracted from selected studies

RESULTS

Literature search results

As per Figure 2, the literature search ultimately yielded a total of 104 intervention studies that reported the amount of therapy provided. A further eight articles meeting inclusion criteria were identified by searching bibliographies of the included studies. A total of 112 papers are included in this review (Appendix 1).[17, 19, 20, 25, 31, 32, 41-146] A subgroup of 14 papers emerged which examined dose-response by comparing the administration of different amounts of the same intervention across groups or individuals (Appendix 2).[17, 20, 25, 43, 49, 65, 79, 81, 86, 100, 106, 113, 133, 136]

294 ***Study characteristics***

295 *Year of publication*

296 Year of publication ranged from 1969 to 2019 (Figure 3). The year with the most published
297 articles in this yield was 2018 (n = 14). The subgroup papers were published between 2005
298 and 2019.

299

300 *Figure 3 Number of publications by year of publication*

301

302 *Sample size*

303 In total, studies reported data from 2,128 individuals with post-stroke aphasia (median n = 8).
304 Sixty-seven studies (60%) reported on 10 participants or fewer (Figure 4). Of these, 17
305 studies involved a single participant. Some individual participants with aphasia were included
306 in more than one published paper. For example, Cherney provided a secondary analysis of
307 data from a subgroup of participants previously reported in Lee and colleagues[17, 100]. There
308 are several other cases of participant duplication within the overall total.[44, 68, 69, 75, 76, 109]

309

310 *Figure 4 Number of publications by sample size*

311

312 *Time post-onset*

313 Studies were categorised by the critical time points of recovery proposed by the Stroke
314 Rehabilitation and Recovery Roundtable[147] with one modification: early and late sub-acute
315 epochs were combined as 'subacute'. This reflects historic reporting of time post-onset in the
316 aphasia literature and reporting within the included studies.

317 All studies reported time post-onset. The vast majority of studies (n = 86) involved
318 participants in the chronic phase of recovery (Figure 5). Five studies involved participants

recruited during the acute phase and eight studies during the subacute phase. A number of studies included participants across multiple phases of recovery; acute to subacute (n = 4), subacute to chronic (n = 4), and acute to chronic (n = 5).

Figure 5 Number of publications by time post-onset and primary outcome

Reported outcome measures

Outcome measures were classified according to the International Classification of Functioning, Disability, and Health (ICF).[148] In excess of 90 outcome measures were reported in this yield. The majority of papers in this review used a measure of impairment-level language function (Figure 5). A small number of papers reported activity- and participation-level communication measures. Very few studies reported measures of wellbeing, quality of life, or participant satisfaction.

Primary outcome measures

Seventy-nine percent of studies (n = 89) use at least one measure of language impairment (as demonstrated on standardised aphasia tests or non-standardised probes of linguistic functions) as the primary outcome measure, 18% of papers (n = 20) use measures of communication activity/participation via functional real-life use of language in connected speech, discourse analysis techniques, or communication rating scales, and 3% (n = 3) report both impairment and activity/participation measures as co-primary outcomes.

Secondary measures

Due to the substantial variability across the included studies, secondary measures will be described in terms of relative frequency. Studies in this review used omnibus aphasia

batteries to classify aphasia type and severity. A large number of language function measures are reported. Many studies report use of customised measures of impairment, particularly naming batteries, tailored to suit specific participants and treatments. Frequently reported surrogate measures of functional communication skills include the Communicative Effectiveness Index[149] and the Communicative Activity Log[31]. A variety of non-linguistic measures used to determine presence and severity of comorbid cognitive dysfunction are reported, with the Raven's Coloured Progressive Matrices[150] by far the most frequently reported. Measures of quality of life (e.g., Stroke and Aphasia Quality of Life Scale – 39),[151] well-being, and patient satisfaction (e.g., Communication Outcomes After STroke)[152] are only occasionally reported. A small number of assessment tools used to identify concomitant motor-speech impairment are also reported.

Study design

A variety of study designs were retrieved (Figure 6). The majority of studies report single-subject methodologies as defined by the Risk of Bias in N-of-1 Trials (RoBiNT) scale.[153] Aligned with the RoBiNT scale, we have differentiated between single-case experimental designs (SCED, n = 12) which can demonstrate cause-effect relationships between the intervention and changes in the target behaviour, and other single-subject methodologies including quasi-experimental single-case AB designs, and non-experimental pre-post designs and case studies (n = 64) which cannot unequivocally demonstrate treatment effect due to a lack of experimental control.[153] Randomised controlled trials (RCT, n = 25) and non-

randomised controlled trials (Non-RCT, n = 11) constitute approximately one third of the yield.

Figure 6 Number of studies by study design

Total doses reported in the yield

Unsurprisingly, the majority of studies in this yield report dose as the number of hours or sessions of treatment provided (Figure 7), or both. Approximately one quarter (27%) report therapeutic inputs, usually the number of times stimulus items were presented over the intervention period, or client acts, most commonly in the form of response accuracy. Three studies in this review report time-on-task, a measure of the time spent actively engaged in treatment during a session.

Figure 7 Number of studies reporting specific dose variables

It is difficult to get an accurate picture of how much treatment is provided in aphasia intervention studies due to inconsistent measurement and reporting of dose parameters. Many studies report the treatment schedule such that the prescribed dose can be calculated, but this is not always the case. Furthermore, the prescribed dose may differ to the actual dose that participants receive due to participants missing or refusing treatment sessions. The table in Appendix 1, therefore, lists the total dose that was either prescribed, actually provided, or estimated based on the treatment schedule reported in each study.

Prescribed hours of treatment ranged from one hour to 100 hours.[55, 108] The most frequently prescribed dose of 30 hours is reported in 16 studies (14%), reflective of the prevalence of treatment schedules that follow Pulvermuller and colleagues' seminal CIAT

schedule.[31] Dose as a count of therapeutic elements may be incomparable across interventions due to probable differences in active ingredients of different therapies; however, the maximum reported dose in a lexical retrieval paradigm comes from Rieu and colleagues who provided 4,000 therapeutic inputs over 10 sessions in a cued naming protocol while Knollman-Porter and colleagues provided 8,400 therapeutic inputs to one participant over 20 sessions in a word-picture verification task designed to improve auditory comprehension.[93, 126]

Adjuvant treatments

In clinical aphasia research, adjuvant treatments are provided to participants with the goal of enhancing the effectiveness of the primary intervention. A number of approaches designed to stimulate aphasia recovery are reported in this yield including non-invasive (n = 4) and invasive brain stimulation (n = 1), pharmacology (n = 5), and physical exercise (n = 1). None of the studies reporting adjuvant treatments made comparisons between different doses of the primary behavioural intervention.

DISCUSSION

This scoping review yielded papers reporting on 50 years of post-stroke aphasia intervention. These studies comprise single-subject methodologies through to large-scale RCTs. Participants were most often in the chronic phase of recovery and interventions predominantly targeted impairment-level linguistic skills with fewer interventions specifically designed to improve communication activity and participation. A vast array of outcome measures was reported in this yield, consistent with previous reviews demonstrating a plethora of measures used in the aphasia literature.[154] The results will now be discussed as they relate to the main research question addressed in this review.

In the post-stroke aphasia literature, how is treatment dose conceptualised, measured and reported?

Dose conceptualisation

Researchers undertaking the studies in this review have conceptualised dose in one of two ways: either as a measure of the continuous variable *time* or as a count of discrete variables, i.e., *therapeutic elements*. Baker's dose and intensity parameter model provides a framework which can be applied to post-stroke aphasia interventions.[14]

A potentially beneficial elaboration of Baker's model of dose parameters would be to clarify the distinction between different dose variables. Figure 8 demonstrates that *dose* could be conceptualised as a specific element of a particular therapy (discrete variable), as a measure of time (continuous variable), or both. Well-defined interventions that target a particular language function, for example, semantic feature analysis (SFA), would be best served by measuring dose in terms of the number of therapeutic elements provided over the course of treatment (i.e., total dose [elements] = session dose [elements] x session frequency x total intervention duration). Alternatively, interventions that utilise multiple therapy approaches per session or social approach therapies where improved communicative exchanges are facilitated through strategy use and/or environmental enhancement (e.g., supported conversation training) may be best suited to quantifying total dose as a product of time (i.e., total dose [hours] = session dose [minutes] x session frequency x total intervention duration), unless the component tasks (e.g., SFA, conversational scripts, strategy-use training module tasks, etc) could be isolated, quantified, and tallied separately.

Figure 8 Dose conceptualised as either a discrete variable or a continuous variable or both, based on Baker (2012)

It remains unclear whether the way in which dose is conceptualised has any effect on the interpretation of treatment effectiveness. Further examination and comparison of both discrete and continuous dose variables will promote greater understanding of how, and for whom, post-stroke aphasia interventions work.

Dose measurement and reporting

There is inconsistent measurement and reporting of dose in the aphasia intervention literature. The majority of these studies measure and report the total duration of treatment prescribed or provided while fewer studies report total dose as a sum of therapeutic elements (e.g., total number of therapeutic inputs provided or client acts performed). It is surprising that only three studies in this review report the more refined measure of time-on-task considering the relative ease with which computer-assisted or computer-delivered treatments could capture this measure. As previously stated, measuring total dose in hours eliminates the opportunity to examine responses to specific therapeutic elements, the active ingredients of intervention. Optimal delivery of active ingredients will enhance service delivery and patient outcomes. It is tempting therefore to home in on the therapeutic elements of complex behavioural interventions in order to examine and evaluate dose-response relationships. However, a number of issues regarding measurement and reporting of dose parameters prevail in the post-stroke aphasia literature.

Therapeutic elements are not routinely measured or reported

There have been many missed opportunities for capturing and reporting discrete therapeutic elements from small-scale single-subject designs to large RCTs. For example, the SP-I-R-IT study purported to be dose-controlled, in that both the intensive and regular groups received 100 hours of therapy.[108] The authors acknowledge that, while participants did on average receive similar total dose hours, examination of discrete therapeutic elements would have allowed more fine-grained analysis of treatment effects. Additionally, in both research and clinical practice total treatment dose is frequently augmented through the provision of self-administered home-based therapy.[101] Increasingly, the feasibility and effectiveness of self-directed computer- or tablet-based treatments is being explored.[97, 155] While prescribed treatment schedules are routinely reported in these studies, the reliability of participants' compliance with practice schedules is rarely reported. As Kurland and colleagues note: "Future studies of the benefits of [home practice] should take advantage of technological advances in mobile health technology … that can allow for remote monitoring, video/audio collection of speech samples, reaction time, practice time, and remote adjustment of task difficulty."[97]

Discrete therapeutic elements are reported but not analysed

In this yield of studies, particularly those reporting naming interventions, the number of stimulus items, cues, accurate responses, inaccurate responses, and self-corrected responses are often reported. In addition to reporting the number of stimuli and protocolised cues used, there is an opportunity to examine the dose-response relationship for individual participant outcomes with regard to these therapeutic elements.[65, 79]

Furthermore, naming studies vary in the way that stimuli and naming attempts are balanced. For example, Fillingham and colleagues found that the number of naming attempts

correlates with picture naming accuracy, a finding replicated by DeDe and colleagues albeit under very different treatment conditions.[65, 71] However, Snell and colleagues found that the size of stimulus sets correlates with the number of words learned in therapy and that this correlation was not affected by aphasia severity.[133] The optimal balance between the number of stimuli and the number of practice opportunities thus remains to be resolved. There are also unanswered questions regarding how stimulus items should be distributed within sessions to enhance learning of individual items. As Dignam and colleagues postulated, distributed practice may enhance new word learning and maintenance of treatment gains.[156] The effect of spaced retrieval within individual treatment sessions needs to be systematically explored.

Current reporting guidelines (e.g., TIDieR) need to be extended to encourage systematic measurement and reporting of dose variables and treatment schedules. Routine analysis will contribute to the identification and exploration of key therapeutic elements and, thus, a deeper understanding of how, and for whom, behavioural interventions work.

Different doses across participants/groups are not analysed

The amount of therapy participants receive often deviates from the treatment protocol due to factors beyond experimental control (e.g., participant withdrawal, missed treatment sessions, etc). For example, Wenke and colleagues describe their pilot RCT in which participants received either four or eight hours per week of a comprehensive aphasia treatment program over eight weeks.[143] The two groups received different total hours of treatment (i.e., 32 vs 64 hours); however, no formal between-group analyses of participant outcomes was performed due to unanticipated withdrawals, small sample size, and participant heterogeneity. Therefore, possible dose-response relationships were not examined. Likewise, the two groups examined by Rodriguez and colleagues received different doses but the groups were pooled

for analysis of treatment effects,[32] thereby obscuring possible between-group dose-related differences.

In summary, *dose* has been conceptualised as both a discrete variable and a continuous variable in aphasia interventions. The measurement and reporting of dose parameters is inconsistent across the post-stroke aphasia intervention literature. A model for conceptualising and measuring dose parameters exists, yet has not been routinely employed in the reporting of results. Reporting guidelines should be extended to encourage researchers to provide more detail regarding treatment dose parameters. More consistent measurement and reporting will allow for more rigorous synthesis of findings and comparison between different interventions which may lead to increased treatment effectiveness and efficiency and, ultimately, better outcomes for people recovering from post-stroke aphasia.

Additional emerging factor: Therapy studies may be under-dosed

A common refrain in the aphasia literature is that interventions are often administered at doses too low to stimulate the neural reorganisation thought to underlie behaviour change.[106] It is open to conjecture just how far below optimal dose current therapy regimes are. The idea of *dose ranging*, where doses are escalated until the point at which the side-effects of intervention outweigh the benefits of participation, may be new to behavioural interventions in stroke rehabilitation. There are no published reports of dose ranging studies in aphasia. While some studies in this review report doses of up to 100 hours[108] and 108 sessions,[69] such high doses are uncommon. The current clinical reality is that 100 hours of treatment is rarely feasible due to costs and logistics, and may not be tolerable or agreeable to many people with aphasia. High dose of therapeutic elements need not equate to prolonged intervention periods. An obvious solution is to increase session dose of the active ingredients of therapy. There is

preliminary evidence to suggest that gains in language and communication functions can be achieved with relatively brief interventions. For example, picture naming accuracy and discourse-level word retrieval can improve to statistically significant levels and be maintained after just one treatment session for some people with aphasia.[55, 81]

Additional emerging factor: Intervention tolerance

A balance between the effort required to engage in treatment and the potential reward of improved language and communication skills needs to be negotiated on a person-by-person basis. Treatment schedules that provide large amounts of therapy over a long duration may not be tolerable or even preferable for all people with aphasia.

Person-level factors that influence intervention tolerance and expectations of recovery need to be considered.[17] For example, tolerance may be mediated by time post-onset, concurrent medical and cognitive comorbidities, fatigue, psychosocial and interpersonal factors, adjustment and grief associated with change of identity and loss of function, and personality traits.[117] Signs that a person is not tolerating treatment may include withdrawal or refusal to receive treatment,[12] degraded performance of an established skill due to "reactive impedance" (i.e., boredom, mental fatigue, inattention, and deficient processing),[157] or reduced patient satisfaction with treatment.[93]

Treatment-related variables such as difficulty of therapy tasks, and the dose and intensity of treatment schedules may also impact tolerance. Time constraints affecting access to clinical services and costs associated with prolonged treatment necessitate the development of efficient models of care. Furthermore, expediated recovery to acceptable levels of function may allow people with aphasia to return to preferred activities sooner with obvious implications for enhanced well-being.

There were no attempts to determine the maximum tolerable dose of any aphasia intervention in the studies included in this review. Signals are emerging from the acute and subacute periods that total doses in excess of 60 hours may not be tolerable for people during this phase of recovery from stroke.[43, 49] In the chronic phase, an upper limit has not been established for high dose, high frequency interventions, including those that provide very high session dose.[81, 126] There is evidence in the literature of selective exclusion of participants from clinical trials due to a predicted inability to tolerate prescribed interventions; however little or no discussion of the predictive determinants driving these decisions is reported.[25] Further exploration of the person- and treatment-specific factors likely to impact intervention tolerance is required. Clear delineation of these factors will enable enhanced treatment prescription and individual recovery from post-stroke aphasia.

Future directions for research on post-stroke aphasia treatment

Synthesis of findings from dose comparison studies

Fourteen papers in this yield explored dose-response relationships by comparing groups or individuals who received different amounts of the same therapy throughout a prescribed intervention period, with mixed findings (Appendix 2). Few studies set out to systematically compare dose-response relationships; rather, the majority performed exploratory post-hoc statistical analysis after finding participants received different doses throughout the treatment schedule. However, future synthesis of the findings from these reports, where possible, may reveal important signals regarding dose-response relationships in post-stroke aphasia interventions.

Consensus definitions for dose parameters in aphasia interventions are required

Inconsistent measurement and reporting of dose parameters across the aphasia literature stems from a lack of standard definitions. The terminology in the existing model provided by Baker lays the foundation for discussions regarding dose and intensity parameters.[14] Consistent use of terminology will have important implications for the development, implementation, and evaluation of dose and intensity studies, for synthesis of data across these studies, for the theoretical exploration of what drives treatment response in these interventions, for clinical decision-making regarding service delivery, and for health policy makers. Once consensus definitions are in place, reporting guidelines (e.g., TIDieR) need to be extended to encourage systematic routine measurement and reporting of dose variables and treatment schedules.

Dose ranging and maximum tolerable dose

Upper limits of dose have yet to be established across the post-stroke recovery continuum. There is a pressing need to determine upper dose limits of aphasia interventions through incremental escalation studies across the critical timepoints of recovery following stroke. The amount of time and effort expended to achieve a clinically significant and worthwhile change in language skills or communication function requires close consultation with participants to determine the criteria by which to define optimal treatment outcome. Future intervention studies should drive improved language and communication outcomes in post-stroke aphasia through systematic dose ranging studies across a range of aphasia interventions. A number of treatment approaches, particularly those targeting lexical retrieval, are ready for this level of exploration.

608 ***Limitations***

609 The question at the base of this review is broad, in line with scoping review methodology.
610 However, it is acknowledged that the studies included for review represent a small subset of
611 the aphasia intervention literature. Lack of consensus on terminology and dose parameter
612 reporting standards may also mean that some relevant studies may have been missed. This
613 review did not attempt to systematically evaluate the quality of the evidence due to the large
614 yield and limited resources available to perform this task, nor was the data extraction chart
615 checked for accuracy by a second reviewer.

616 The final major limitation is that treatment dose is invariably confounded with
617 treatment *intensity*.[158] In the aphasia literature, intensity has come to be synonymous with
618 *frequency* and means the rate at which a particular dose is provided: it is the quotient of dose
619 over time. Dose and intensity are, therefore, interdependent. When evaluating interventions,
620 we are faced with the issue of determining which parameter, if any, confers the treatment
621 effect. It is possible, perhaps probable, that the overall impact on outcome is a result of the
622 interaction between a number of these variables.[159] Further research is required to compare
623 and contrast the relative effects of treatment dose and treatment intensity.

624

625 **CONCLUSION**

626 Treatment dose is an important parameter of post-stroke aphasia interventions. Most aphasia
627 intervention studies report the total number of treatment hours or sessions provided rather
628 than counts of therapeutic elements. A conceptual framework for describing and reporting
629 discrete therapeutic elements exists and, with sufficient uptake, will improve consistency of
630 measurement and reporting across aphasia treatment trials. At present, inconsistent
631 measurement and reporting of dose may hamper systematic synthesis of findings across
632 intervention studies. Nevertheless, there is emerging evidence of dose-response relationships

in a small number of studies. However, studies employ a wide variety of treatment schedules (i.e., session dose, session frequency, and intervention duration) and the particular combination of these may also impinge on the relationship between efficacy and total dose. High dose interventions delivered over short intervention periods may improve treatment efficiency. Person- and treatment-level factors that mediate tolerance of high dose interventions require further investigation. Further systematic exploration of dose-response relationships in post-stroke aphasia treatment is required.

Funding

This work was supported by an Australian Government Research Training Program Scholarship and the NHMRC funded Centre for Research Excellence in Aphasia Recovery and Rehabilitation (#1153236).

646 Bibliography

647

648 1 Engelter, S. T., et al., (2006). Epidemiology of aphasia attributable to first ischemic
649 stroke: incidence, severity, fluency, etiology, and thrombolysis. *Stroke, 37*(6): p.
650 1379-1384.

651 2 El Hachioui, H., et al., (2013). Long-term prognosis of aphasia after stroke. *J Neurol*
652 *Neurosurg Psychiatry, 84*(3): p. 310-315.

653 3 Hilari, K., Needle, J. J., and Harrison, K. L., (2012). What are the important factors in
654 health-related quality of life for people with aphasia? A systematic review. *Archives*
655 *of physical medicine and rehabilitation, 93*(1): p. S86-S95.

656 4 Pedersen, P. M., Vinter, K., and Olsen, T. S., (2004). Aphasia after stroke: type,
657 severity and prognosis. *Cerebrovascular Diseases, 17*(1): p. 35-43.

658 5 Laska, A. C., et al., (2001). Aphasia in acute stroke and relation to outcome. *Journal*
659 *of internal medicine, 249*(5): p. 413-422.

660 6 Ellis, C., et al., (2012). The one-year attributable cost of poststroke aphasia. *Stroke,*
661 *43*(5): p. 1429-1431.

662 7 Dickey, L., et al., (2010). Incidence and profile of inpatient stroke-induced aphasia in
663 Ontario, Canada. *Archives of physical medicine and rehabilitation, 91*(2): p. 196-202.

664 8 Lam, J. M. C. and Wodchis, W. P., (2010). The relationship of 60 disease diagnoses
665 and 15 conditions to preference-based health-related quality of life in Ontario
666 hospital-based long-term care residents. *Medical care*: p. 380-387.

667 9 Simmons-Mackie, N. and Kagan, A., (2007). Application of the ICF in aphasia. *28*(4):
668 p. 244-253.

669 10 Allen, L., et al., (2012). Therapeutic interventions for aphasia initiated more than six
670 months post stroke: a review of the evidence. *Topics in Stroke Rehabilitation, 19*(6):
671 p. 523-535.
672 11 Basso, A., (2005). Language deficits: The efficacy of the impairment-based treatment.
673 *Effectiveness of rehabilitation for cognitive deficits.*: p. 185-194.
674 12 Brady, M., et al., (2016). Speech and Language Therapy (SLT) for aphasia after
675 stroke: cochrane systematic review evidence of therapy regimens, delivery models
676 and theoretical approaches. *European stroke journal, 1*(1): p. 693-.
677 13 Robey, R. R., (1998). A meta-analysis of clinical outcomes in the treatment of
678 aphasia. *J Speech Lang Hear Res, 41*(1): p. 172-87.
679 14 Baker, E., (2012). Optimal intervention intensity. *International Journal of Speech-*
680 *Language Pathology, 14*(5): p. 401-409.
681 15 Kiran, S. and Thompson, C. K., (2019). Neuroplasticity of Language Networks in
682 Aphasia: Advances, Updates and Future Challenges. *Frontiers in neurology, 10*: p.
683 295.
684 16 Dalton, E. J., et al., (2019). Dose Articulation in Preclinical and Clinical Stroke
685 Recovery: Refining a Discovery Research Pipeline and Presenting a Scoping Review
686 Protocol. *Frontiers in Neurology, 10*: p. 1148.
687 17 Cherney, L. R., (2012). Aphasia treatment: intensity, dose parameters, and script
688 training. *Int J Speech Lang Pathol, 14*(5): p. 424-31.
689 18 Warren, S. F., Fey, M. E., and Yoder, P. J., (2007). Differential treatment intensity
690 research: A missing link to creating optimally effective communication interventions.
691 *Mental retardation and developmental disabilities research reviews, 13*(1): p. 70-77.

19 Dignam, J., et al., (2015). Intensive versus distributed aphasia therapy: a non-randomised, parallel-groups, dosage-controlled study. *International journal of stroke, 10*: p. 13-14.

20 Off, C. A., et al., (2016). The impact of dose on naming accuracy with persons with aphasia. *Aphasiology, 30*(9): p. 983-1011.

21 Turkstra, L., Rocio, N., Whyte, J., Dijkers, M. P., Hart, T., (2016). Knowing What We're Doing: Why Specification of Treatment Methods Is Critical for Evidence-Based Practice in Speech-Language Pathology. *American Journal of Speech-Language Pathology, 25*: p. 164-171.

22 Cherney, L. R., Patterson, J. P., and Raymer, A. M., (2011). Intensity of aphasia therapy: evidence and efficacy. *Curr Neurol Neurosci Rep, 11*(6): p. 560-9.

23 Bhogal, S. K., Teasell, R., and Speechley, M., (2003). Intensity of aphasia therapy, impact on recovery. *Stroke, 34*(4): p. 987-93.

24 Hoffmann, T. C., et al., (2014). Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *Bmj, 348*: p. g1687.

25 Carpenter, J. and Cherney, L. R., (2016). Increasing aphasia treatment intensity in an acute inpatient rehabilitation programme: a feasibility study. *Aphasiology, 30*(5): p. 542-565.

26 Bowen, A., et al., (2012). Effectiveness of enhanced communication therapy in the first four months after stroke for aphasia and dysarthria: a randomised controlled trial. *Bmj, 345*: p. e4407.

27 Rose, M. L., Cherney, L. R., and Worrall, L. E., (2013). Intensive comprehensive aphasia programs: An international survey of practice. *Topics in Stroke Rehabilitation, 20*(5): p. 379-387.

28 Walker, M. F., et al., (2017). Improving the development, monitoring and reporting of stroke rehabilitation research: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. *International Journal of Stroke, 12*(5): p. 472-479.

29 Justice, L. M., (2018). Conceptualising "dose" in paediatric language interventions: Current findings and future directions. *International journal of speech-language pathology, 20*(3): p. 318-323.

30 Rose, M. L., et al., (2013). Multi-modality aphasia therapy is as efficacious as a constraint-induced aphasia therapy for chronic aphasia: A phase 1 study. *Aphasiology, 27*(8): p. 938-971.

31 Pulvermuller, F., et al., (2001). Constraint-induced therapy of chronic aphasia after stroke. *Stroke, 32*(7): p. 1621-6.

32 Rodriguez, A. D., et al., (2013). Aphasia LIFT: Exploratory investigation of an intensive comprehensive aphasia programme. *Aphasiology, 27*(11): p. 1339-1361.

33 Hickok, G., (2009). The functional neuroanatomy of language. *Physics of life reviews, 6*(3): p. 121-143.

34 Quique, Y. M., Evans, W. S., and Dickey, M. W., (2019). Acquisition and Generalization Responses in Aphasia Naming Treatment: A Meta-Analysis of Semantic Feature Analysis Outcomes. *Am J Speech Lang Pathol, 28*(1): p. 230-246.

35 Nardo, D., et al., (2017). Less is more: neural mechanisms underlying anomia treatment in chronic aphasic patients. *Brain, 140*(11): p. 3039-3054.

36 Arksey, H. and O'Malley, L., (2005). Scoping studies: towards a methodological framework. *International journal of social research methodology, 8*(1): p. 19-32.

37 Levac, D., Colquhoun, H., and O'Brien, K. K., (2010). Scoping studies: advancing the methodology. *Implementation science, 5*(1): p. 69.

38 Peters, M. D. J., et al., (2015). Guidance for conducting systematic scoping reviews. *International journal of evidence-based healthcare, 13*(3): p. 141-146.

39 Tricco, A. C., et al., (2018). PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Annals of internal medicine, 169*(7): p. 467-473.

40 Liberati, A., et al., (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS medicine, 6*(7): p. e1000100.

41 Abo, M., et al., (2012). Effectiveness of low-frequency rTMS and intensive speech therapy in poststroke patients with aphasia: a pilot study based on evaluation by fMRI in relation to type of aphasia. *Eur Neurol, 68*(4): p. 199-208.

42 Aerts, A., et al., (2015). Aphasia therapy early after stroke: behavioural and neurophysiological changes in the acute and post-acute phases. *Aphasiology, 29*(7): p. 845-871.

43 Bakheit, A. M. O., et al., (2007). A prospective, randomized, parallel group, controlled study of the effect of intensity of speech and language therapy on early recovery from poststroke aphasia. *Clinical Rehabilitation, 21*(10): p. 885-894.

44 Barthel, G., et al., (2008). Intensive language therapy in chronic aphasia: which aspects contribute most? *Aphasiology, 22*(4): p. 408-421.

45 Berthier, M. L., et al., (2017). Cholinergic Potentiation and Audiovisual Repetition-Imitation Therapy Improve Speech Production and Communication Deficits in a Person with Crossed Aphasia by Inducing Structural Plasticity in White Matter Tracts. *Front Hum Neurosci, 11*: p. 304.

46 Berthier, M. L., et al., (2009). Memantine and constraint-induced aphasia therapy in chronic poststroke aphasia. *Annals of Neurology, 65*(5): p. 577-585.

766 47 Biran, M. and Fisher, S., (2015). Structured treatment can improve predicate
767 argument structure impairment. *Aphasiology, 29*(1): p. 29-56.
768 48 Bose, A., (2013). Phonological therapy in jargon aphasia: effects on naming and
769 neologisms. *Int J Lang Commun Disord, 48*(5): p. 582-95.
770 49 Breitenstein, C., et al., (2017). Intensive speech and language therapy in patients with
771 chronic aphasia after stroke: A randomised, open-label, blinded-endpoint, controlled
772 trial in a health-care setting. *The Lancet, 389*(10078): p. 1528-1538.
773 50 Breitenstein, C., et al., (2015). L-dopa does not add to the success of high-intensity
774 language training in aphasia. *Restorative neurology and neuroscience, 33*(2): p. 115-
775 120.
776 51 Brookshire, C. E., et al., (2014). Effects of Intensive Phonomotor Treatment on
777 Reading in Eight Individuals With Aphasia and Phonological Alexia. *American*
778 *Journal of Speech-Language Pathology, 23*(2): p. S300-11.
779 52 Carragher, M., Sage, K., and Conroy, P., (2013). The effects of verb retrieval therapy
780 for people with non-fluent aphasia: evidence from assessment tasks and conversation.
781 *Neuropsychol Rehabil, 23*(6): p. 846-87.
782 53 Carragher, M., Sage, K., and Conroy, P., (2015). Preliminary analysis from a novel
783 treatment targeting the exchange of new information within storytelling for people
784 with nonfluent aphasia and their partners. *Aphasiology, 29*(11): p. 1383-1408.
785 54 Cherney, L., (2010). Oral Reading for Language in Aphasia (ORLA): Evaluating the
786 efficacy of computer-delivered therapy in chronic nonfluent aphasia. *Topics in Stroke*
787 *Rehabilitation, 17*(6): p. 423-431.
788 55 Cherney, L. R., et al., (2019). Optimising recovery in aphasia: Learning following
789 exposure to a single dose of computer-based script training. *International Journal of*
790 *Speech-Language Pathology*: p. 1-11.

56 Cherney, L. R., et al., (2012). Epidural cortical stimulation and aphasia therapy. *Aphasiology, 26*(9): p. 1192-1217.

57 Cherney, L. R., Merbitz, C. T., and Grip, J. C., (1986). Efficacy of oral reading in aphasia treatment outcome. *Rehabilitation Literature, 47*(5): p. 112-118.

58 Ciccone, N., et al., (2016). Constraint-induced aphasia therapy (CIAT): a randomised controlled trial in very early stroke rehabilitation. *Aphasiology, 30*(5): p. 566-584.

59 Conley, A. and Coelho, C. A., (2003). Treatment of word retrieval impairment in chronic Broca's aphasia. *Aphasiology, 17*(3): p. 203-211.

60 Conroy, P., et al., (2012). Decreasing cues for a dynamic list of noun and verb naming targets: a case-series aphasia therapy study. *Neuropsychological Rehabilitation, 22*(2): p. 295-318.

61 Conroy, P., Sage, K., and Ralph, M. A. L., (2009). A comparison of word versus sentence cues as therapy for verb naming in aphasia. *Aphasiology, 23*(4): p. 462-482.

62 Cotelli, M., et al., (2011). Anomia training and brain stimulation in chronic aphasia. *Neuropsychological Rehabilitation, 21*(5): p. 717-741.

63 Crerar, M. A., Ellis, A. W., and Dean, E. C., (1996). Remediation of sentence processing deficits in aphasia using a computer-based microworld. *Brain Lang, 52*(1): p. 229-75.

64 Cunningham, R. and Ward, C. D., (2003). Evaluation of a training programme to facilitate conversation between people with aphasia and their partners. *Aphasiology, 17*(8): p. 687-707.

65 DeDe, G., Hoover, E., and Maas, E., (2019). Two to Tango or the More the Merrier? A Randomized Controlled Trial of the Effects of Group Size in Aphasia Conversation Treatment on Standardized Tests. *J Speech Lang Hear Res, 62*(5): p. 1437-1451.

66 Des Roches, C. A., Mitko, A., and Kiran, S., (2017). Relationship between Self-Administered Cues and Rehabilitation Outcomes in Individuals with Aphasia: Understanding Individual Responsiveness to a Technology-Based Rehabilitation Program. *Front Hum Neurosci, 11*: p. 07.

67 Dignam, J., et al., (2016). The relationship between novel word learning and anomia treatment success in adults with chronic aphasia. *Neuropsychologia, 81*: p. 186-197.

68 Duncan, E. S. and Small, S. L., (2017). Imitation-based aphasia therapy increases narrative content: a case series. *Clinical rehabilitation, 31*(11): p. 1500-1507.

69 Duncan, E. S. and Small, S. L., (2018). Changes in dynamic resting state network connectivity following aphasia therapy. *Brain Imaging Behav, 12*(4): p. 1141-1149.

70 Faroqi-Shah, Y. and Virion, C. R., (2009). Constraint-induced language therapy for agrammatism: role of grammaticality constraints. *Aphasiology, 23*(7): p. 977-988.

71 Fillingham, J., Sage, K., and Lambon Ralph, M., (2005). Further explorations and an overview of errorless and errorful therapy for aphasic word-finding difficulties: The number of naming attempts during therapy affects outcome. *Aphasiology, 19*(7): p. 597-614.

72 Floel, A., et al., (2011). Short-term anomia training and electrical brain stimulation. *Stroke, 42*(7): p. 2065-7.

73 Furnas, D. W. and Edmonds, L. A., (2014). The effect of computerised Verb Network Strengthening Treatment on lexical retrieval in aphasia. *Aphasiology, 28*(4): p. 401-420.

74 Galling, M. A., et al., (2014). A clinical study of the combined use of bromocriptine and speech and language therapy in the treatment of a person with aphasia. *Aphasiology, 28*(2): p. 171-187.

839 75 Godecke, E., et al., (2014). A comparison of aphasia therapy outcomes before and
840 after a Very Early Rehabilitation programme following stroke. *Int J Lang Commun*
841 *Disord, 49*(2): p. 149-61.
842 76 Godecke, E., et al., (2012). Very early poststroke aphasia therapy: a pilot randomized
843 controlled efficacy trial. *Int J Stroke, 7*(8): p. 635-44.
844 77 Goodkin, R., (1969). Changes in word production, sentence production and relevance
845 in an aphasic through verbal conditioning. *Behaviour Research and Therapy, 7*(1): p.
846 93-99.
847 78 Goral, M. and Kempler, D., (2009). Training verb production in communicative
848 context: Evidence from a person with chronic non-fluent aphasia. *Aphasiology,*
849 *23*(12): p. 1383-1397.
850 79 Gravier, M. L., et al., (2018). What matters in semantic feature analysis: Practice-
851 related predictors of treatment response in aphasia. *American Journal of Speech-*
852 *Language Pathology, 27*(1S): p. 438-453.
853 80 Griffith, J., et al., (2017). An examination of changes in spoken productions within
854 constraint-induced aphasia therapy. *Aphasiology, 31*(11): p. 1250-1265.
855 81 Harnish, S. M., et al., (2013). Dosing of a Cued Picture-Naming Treatment for
856 Anomia. *American Journal of Speech-Language Pathology, 23*(2): p. S285-99.
857 82 Harnish, S. M., et al., (2008). Use of fMRI in the study of chronic aphasia recovery
858 after therapy: a case study. *Topics in Stroke Rehabilitation, 15*(5): p. 468-483.
859 83 Harnish, S. M., et al., (2018). Aerobic Exercise as an Adjuvant to Aphasia Therapy:
860 Theory, Preliminary Findings, and Future Directions. *Clin Ther, 40*(1): p. 35-48.e6.
861 84 Hartman, J. and Landau, W. M., (1987). Comparison of formal language therapy with
862 supportive counseling for aphasia due to acute vascular accident. *Archives of*
863 *neurology, 44*(6): p. 646-649.

85 Helmick, J. W. and Wipplinger, M., (1975). Effects of stimulus repetition on the naming behavior of an aphasic adult: a clinical report. *J Commun Disord, 8*(1): p. 23-9.

86 Herbert, R., Webster, D., and Dyson, L., (2012). Effects of syntactic cueing therapy on picture naming and connected speech in acquired aphasia. *Neuropsychol Rehabil, 22*(4): p. 609-33.

87 Hough, M. S., (2010). Melodic Intonation Therapy and aphasia: another variation on a theme. *Aphasiology, 24*(6): p. 775-786.

88 Hough, M. and Johnson, R. K., (2009). Use of ACC to enhance linguistic communication skills in an adult with chronic severe aphasia. *Aphasiology, 23*(7): p. 965-976.

89 Kaviani, S., et al., (2018). Effects of multimodal communication program on patients with chronic aphasia: a single-subject A-B-A design study. *Electron Physician, 10*(3): p. 6439-6447.

90 Kim, E. S. and Lemke, S. F., (2016). Behavioural and eye-movement outcomes in response to text-based reading treatment for acquired alexia. *Neuropsychol Rehabil, 26*(1): p. 60-86.

91 Kirmess, M. and Lind, M., (2011). Spoken language production as outcome measurement following constraint induced language therapy. *Aphasiology, 25*(10): p. 1207-1238.

92 Kirmess, M. and Maher, L. M., (2010). Constraint induced language therapy in early aphasia rehabilitation. *Aphasiology, 24*(6): p. 725-736.

93 Knollman-Porter, K., Dietz, A., and Dahlem, K., (2018). Intensive Auditory Comprehension Treatment for Severe Aphasia: A Feasibility Study. *Am J Speech Lang Pathol, 27*(3): p. 936-949.

889 94 Koyuncu, E., et al., (2016). Speech and language therapy for aphasia following
890 subacute stroke. *Neural Regen Res, 11*(10): p. 1591-1594.
891 95 Krajenbrink, T., Nickels, L., and Kohnen, S., (2017). No effect of orthographic
892 neighbourhood in treatment with two cases of acquired dysgraphia. *Aphasiology,*
893 *31*(5): p. 595-628.
894 96 Kristensen, L. F., et al., (2015). Constraint-induced aphasia therapy in subacute
895 neurorehabilitation. *Aphasiology, 29*(10): p. 1152-1163.
896 97 Kurland, J., Anna, L., and Stokes, P., (2018). Effects of a Tablet-Based Home
897 Practice Program With Telepractice on Treatment Outcomes in Chronic Aphasia.
898 *Journal of Speech, Language & Hearing Research, 61*(5): p. 1140-1156.
899 98 Kurland, J., Baldwin, K., and Tauer, C., (2010). Treatment-induced neuroplasticity
900 following intensive naming therapy in a case of chronic Wernicke's aphasia.
901 *Aphasiology, 24*(6): p. 737-751.
902 99 Kurland, J., et al., (2012). Constrained Versus Unconstrained Intensive Language
903 Therapy in Two Individuals With Chronic, Moderate-to-Severe Aphasia and Apraxia
904 of Speech: Behavioral and fMRI Outcomes. *American Journal of Speech-Language*
905 *Pathology*: p. S65-87.
906 100 Lee, J. B., Kaye, R. C., and Cherney, L. R., (2009). Conversational script
907 performance in adults with non-fluent aphasia: treatment intensity and aphasia
908 severity. *Aphasiology, 23*(7): p. 885-897.
909 101 Lee, J. B., et al., (2018). Attention Process Training-3 to improve reading
910 comprehension in mild aphasia: A single-case experimental design study.
911 *Neuropsychol Rehabil*: p. 1-32.

912 102 Lucchese, G., et al., (2017). Therapy-induced neuroplasticity of language in chronic
913 post stroke aphasia: A mismatch negativity study of (A)grammatical and
914 meaningful/less mini-constructions. *Frontiers in Human Neuroscience, 10*.
915 103 Maher, L. M., et al., (2006). A pilot study of use-dependent learning in the context of
916 Constraint Induced Language Therapy. *Journal of the International*
917 *Neuropsychological Society, 12*(6): p. 843-852.
918 104 Marcotte, K., et al., (2018). Therapy-Induced Neuroplasticity in Chronic Aphasia
919 After Phonological Component Analysis: A Matter of Intensity. *Front Neurol, 9*: p.
920 225.
921 105 Marshall, J., et al., (2016). Evaluating the Benefits of Aphasia Intervention Delivered
922 in Virtual Reality: Results of a Quasi-Randomised Study. *PLoS One, 11*(8): p.
923 e0160381.
924 106 Marshall, J., et al., (2013). Computer delivery of gesture therapy for people with
925 severe aphasia. *Aphasiology, 27*(9): p. 1128-1146.
926 107 Martin, P. I., et al., (2014). Language improvements after TMS plus modified CILT:
927 Pilot, open-protocol study with two, chronic nonfluent aphasia cases. *Restorative*
928 *Neurology and Neuroscience, 32*(4): p. 483-505.
929 108 Martins, I. P., et al., (2013). A randomized, rater-blinded, parallel trial of intensive
930 speech therapy in sub-acute post-stroke aphasia: the SP-I-R-IT study. *International*
931 *Journal of Language & Communication Disorders, 48*(4): p. 421-431.
932 109 Meinzer, M., et al., (2005). Long-term stability of improved language functions in
933 chronic aphasia after constraint-induced aphasia therapy. *Stroke, 36*(7): p. 1462-6.
934 110 Meinzer, M., et al., (2004). Intensive language training enhances brain plasticity in
935 chronic aphasia. *BMC Biol, 2*: p. 20.

111 Meinzer, M., et al., (2007). Functional re-recruitment of dysfunctional brain areas predicts language recovery in chronic aphasia. *Neuroimage, 39*(4): p. 2038-46.

112 Mozeiko, J., Coelho, C. A., and Myers, E. B., (2016). The role of intensity in constraint-induced language therapy for people with chronic aphasia. *Aphasiology, 30*(4): p. 339-363.

113 Mozeiko, J., Myers, E. B., and Coelho, C. A., (2018). Treatment Response to a Double Administration of Constraint-Induced Language Therapy in Chronic Aphasia. *J Speech Lang Hear Res, 61*(7): p. 1664-1690.

114 Munro, P. and Siyambalapitiya, S., (2017). Improved word comprehension in Global aphasia using a modified semantic feature analysis treatment. *Clin Linguist Phon, 31*(2): p. 119-136.

115 Newton, C., Kirby, P., and Bruce, C., (2017). Getting into shape: the effect of Shape Coding on the spoken language production of two men with chronic aphasia. *Aphasiology, 31*(12): p. 1459-1481.

116 Nickels, L. and Osborne, A., (2016). Constraint Induced Aphasia Therapy: Volunteer-led, unconstrained and less intense delivery can be effective. *NeuroRehabilitation, 39*(1): p. 97-109.

117 Nouwens, F., et al., (2017). Early cognitive-linguistic treatment for aphasia due to stroke; A randomised controlled trial (rats- 3). *European Stroke Journal, 2*(1): p. 4.

118 Nykänen, A., et al., (2013). Communication therapy for people with aphasia and their partners (APPUTE). *Aphasiology, 27*(10): p. 1159-1179.

119 Palmer, R., et al., (2019). Self-managed, computerised speech and language therapy for patients with chronic aphasia post-stroke compared with usual care or attention control (Big CACTUS): a multicentre, single-blinded, randomised controlled trial. *The Lancet Neurology, 18*(9): p. 821-833.

120 Peach, R. K., (2002). Treatment for phonological dyslexia targeting regularity effects. *Aphasiology, 16*(8): p. 779-789.

121 Peach, R. K. and Reuter, K. A., (2010). A discourse-based approach to semantic feature analysis for the treatment of aphasic word retrieval failures. *Aphasiology, 24*(9): p. 971-990.

122 Poeck, K., Huber, W., and Willmes, K., (1989). Outcome of intensive language treatment in aphasia. *J Speech Hear Disord, 54*(3): p. 471-9.

123 Ramsberger, G. and Marie, B., (2007). Self-administered cued naming therapy: a single-participant investigation of a computer-based therapy program replicated in four cases. *Am J Speech Lang Pathol, 16*(4): p. 343-58.

124 Raymer, A. M., Kohen, F. P., and Saffell, D., (2006). Computerised training for impairments of word comprehension and retrieval in aphasia. *Aphasiology, 20*(2-4): p. 257-268.

125 Richardson, J., et al., (2015). Feasibility of using high-definition transcranial direct current stimulation (HD-tDCS) to enhance treatment outcomes in persons with aphasia. *NeuroRehabilitation, 36*(1): p. 115-26.

126 Rieu, D., Lorne, F., and Dalla Barba, G., (2001). What is the role of semantics in selective damage to the phonological output lexicon? *Cortex: A Journal Devoted to the Study of the Nervous System and Behavior, 37*(5): p. 727-729.

127 Rogalski, Y., et al., (2013). Attentive Reading and Constrained Summarisation (ARCS) discourse treatment for chronic Wernicke's aphasia. *Aphasiology, 27*(10): p. 1232-1251.

128 Romani, C., et al., (2019). Playing a team game improves word production in poststroke aphasia. *Aphasiology*: p. No-Specified.

129 Rose, M. and Sussmilch, G., (2008). The effects of semantic and gesture treatments on verb retrieval and verb use in aphasia. *Aphasiology, 22*(7): p. 691-706.

130 Rubin, C. and Bollinger, R. L., (1983). Aphasia: Treatment considerations, graphic output. *Topics in Language Disorders, 3*(4): p. 67-75.

131 Sage, K., et al., (2011). How intensive does anomia therapy for people with aphasia need to be? *Neuropsychological Rehabilitation, 21*(1): p. 26-41.

132 Sickert, A., et al., (2014). Constraint-induced aphasia therapy following sub-acute stroke: a single-blind, randomised clinical trial of a modified therapy schedule. *Journal of Neurology, Neurosurgery & Psychiatry, 85*(1): p. 51-55.

133 Snell, C., Sage, K., and Ralph, M. A. L., (2010). How many words should we provide in anomia therapy? A meta-analysis and a case series study. *Aphasiology, 24*(9): p. 1064-1094.

134 Stadie, N., et al., (2008). Unambiguous generalization effects after treatment of non-canonical sentence production in German agrammatism. *Brain & Language, 104*(3): p. 211-229.

135 Stahl, B., et al., (2013). How to engage the right brain hemisphere in aphasics without even singing: evidence for two paths of speech recovery. *Front Hum Neurosci, 7*: p. 35.

136 Stahl, B., et al., (2018). Efficacy of intensive aphasia therapy in patients with chronic stroke: a randomised controlled trial. *J Neurol Neurosurg Psychiatry, 89*(6): p. 586-592.

137 Stahl, B., et al., (2016). Using language for social interaction: Communication mechanisms promote recovery from chronic non-fluent aphasia. *Cortex: A Journal Devoted to the Study of the Nervous System & Behavior, 85*: p. 90-99.

138 Stark, B. C. and Warburton, E. A., (2018). Improved language in chronic aphasia after self-delivered iPad speech therapy. *Neuropsychol Rehabil, 28*(5): p. 818-831.

139 Thiel, L., Sage, K., and Conroy, P., (2016). The role of learning in improving functional writing in stroke aphasia. *Disabil Rehabil, 38*(21): p. 2122-34.

140 van Hees, S., et al., (2014). A functional MRI study of the relationship between naming treatment outcomes and resting state functional connectivity in post-stroke aphasia. *Hum Brain Mapp, 35*(8): p. 3919-31.

141 Vuksanović, J., et al., (2018). Effect of type of language therapy on expressive language skills in patients with post-stroke aphasia. *International journal of language & communication disorders, 53*(4): p. 825-835.

142 Wallace, S. E. and Kayode, S., (2017). Effects of a semantic plus multimodal communication treatment for modality switching in severe aphasia. *Aphasiology, 31*(10): p. 1127-1142.

143 Wenke, R., et al., (2018). Communication and well-being outcomes of a hybrid service delivery model of intensive impairment-based treatment for aphasia in the hospital setting: a pilot study. *Disabil Rehabil, 40*(13): p. 1532-1541.

144 Wieczorek, R., Huber, W., and Darkow, R., (2011). Tense/aspect category in fluent and nonfluent German aphasia: An experimental training programme for verb production. *Aphasiology, 25*(8): p. 851-871.

145 Woldag, H., et al., (2017). Constraint-Induced Aphasia Therapy in the Acute Stage. *Neurorehabilitation & Neural Repair, 31*(1): p. 72-80.

146 Yamada, N., et al., (2016). Atomoxetine administration combined with intensive speech therapy for post-stroke aphasia: evaluation by a novel SPECT method. *Int J Neurosci, 126*(9): p. 829-38.

147 Bernhardt, J., et al., (2017). Agreed definitions and a shared vision for new standards in stroke recovery research: the stroke recovery and rehabilitation roundtable taskforce. *International Journal of Stroke, 12*(5): p. 444-450.

148 World Health Organization, *International classification of functioning, disability and health: ICF*. 2001: Geneva: World Health Organization.

149 Lomas, J., et al., (1989). The communicative effectiveness index: Development and psychometric evaluation of a functional communication measure for adult aphasia. *Journal of speech and hearing disorders, 54*(1): p. 113-124.

150 Kertesz, A. and McCabe, P., (1975). Intelligence and aphasia: Performance of aphasics on Raven's Coloured Progressive Matrices (RCPM). *Brain and Language, 2*: p. 387-395.

151 Hilari, K., et al., (2003). Stroke and aphasia quality of life scale-39 (SAQOL-39) evaluation of acceptability, reliability, and validity. *Stroke, 34*(8): p. 1944-1950.

152 Long, A. F., et al., (2008). Development of a reliable self-report outcome measure for pragmatic trials of communication therapy following stroke: the Communication Outcome after Stroke (COAST) scale. *Clinical Rehabilitation, 22*(12): p. 1083-1094.

153 Tate, R. L., et al., *The Risk-of-Bias in N-of-1 Trials (RoBiNT) scale: An expanded manual for the critical appraisal of single-case reports*. 2015: Robyn Tate.

154 Wallace, S. J., et al., (2019). A core outcome set for aphasia treatment research: The ROMA consensus statement. *International journal of stroke, 14*(2): p. 180-185.

155 Des Roches, C. A. and Kiran, S., (2017). Technology-Based Rehabilitation to Improve Communication after Acquired Brain Injury. *Front Neurosci, 11*: p. 382.

156 Dignam, J. K., Rodriguez, A. D., and Copland, D. A., (2016). Evidence for Intensive Aphasia Therapy: Consideration of Theories From Neuroscience and Cognitive Psychology. *Pm r, 8*(3): p. 254-67.

157 Dail, T. K. and Christina, R. W., (2004). Distribution of practice and metacognition in learning and long-term retention of a discrete motor task. *Research quarterly for exercise and sport, 75*(2): p. 148-155.

158 Doogan, C., et al., (2018). Aphasia Recovery: When, How and Who to Treat? *Curr Neurol Neurosci Rep, 18*(12): p. 90.

159 Togher, L., (2012). Challenges inherent in optimizing speech-language pathology outcomes: It's not just about counting the hours. *International Journal of Speech-Language Pathology, 14*(5): p. 438-442.

Figure and table legend