Treatment-induced neuroplasticity after anomia therapy in post-stroke aphasia: A systematic review of neuroimaging studies

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Abstract

We systematically reviewed the literature pertaining to neural changes following anomia treatment post-stroke. We conducted electronic searches of six databases: CINAHL, Cochrane Trials, Embase, Ovid MEDLINE, MEDLINE-in-Process and PsycINFO; two independent raters assessed all abstracts and full texts. Accepted studies reported original data on adults with post-stroke aphasia, who received behavioural treatment for anomia, and magnetic resonance brain imaging (MRI) pre- and post-treatment. Search results yielded 2481 unique citations; 33 studies were accepted for review. The majority of studies employed functional MRI and the quality of reporting neuroimaging methodology was variable, particularly with respect to pre-processing steps and statistical analyses. The most methodologically robust data were extracted and synthesized with a focus on pre- versus post-treatment contrasts. Studies more commonly reported increases (compared to decreases) in activation following naming therapy, primarily in the left supramarginal gyrus, and the left precuneus. Our findings highlight the methodological heterogeneity across MRI studies, and the relative paucity of robust evidence demonstrating direct links between brain and behaviour in anomia rehabilitation.

Keywords: stroke; aphasia; anomia; treatment; neuroplasticity; magnetic resonance imaging; systematic review

1 Introduction

Stroke is a leading cause of death and disability worldwide (WHO, 2012); in North America alone, roughly 857,000 individuals will suffer a stroke each year (Go et al., 2014; HSF, 2018). Approximately one in three stroke survivors will present with aphasia, a difficulty producing or understanding language (Dickey et al., 2010; Flowers et al., 2016). Although the clinical manifestation of aphasia can differ, one of the most ubiquitous and frustrating symptoms of virtually all aphasia types is anomia, which can lead to impairments in naming objects, pictures, people, or actions. Anomia is thought to arise from difficulties in accessing semantics or phonology, or in accessing and assembling phonemes (Laine & Martin, 2006). Thus, anomia can result from damage to many different brain regions responsible for the various stages of the naming process (DeLeon et al., 2007).

There is a large and growing body of evidence demonstrating the efficacy of behavioural anomia rehabilitation, with studies showing short- and long-term language improvements induced by treatment (e.g., Palmer et al., 2019; Breitenstein et al., 2017; Nickels, 2002; Wisenburn & Mahoney, 2009). Anomia rehabilitation is largely predicated on the fundamental principle that functional changes in behaviour are the result of corresponding changes in the brain (Raskin, 2011; Sohlberg & Mateer, 2001). Neuroplasticity, or the capacity of the brain to continuously re-wire synaptic connections, enables neural activation patterns to be modulated in response to learning (e.g., therapeutic) experiences (Leuner & Gould, 2010; Kleim & Jones, 2008; Raymer et al., 2008). Thus, gaining a deeper understanding of the neural mechanisms underlying anomia recovery may hold great theoretical and clinical importance.

1.1 Magnetic Resonance Imaging in naming and anomia rehabilitation

The development of structural and functional Magnetic Resonance Imaging (MRI) techniques in the last 30 years has revolutionized research in aphasia. Structural MRI approaches have been used extensively to characterize the effect of stroke-induced damage on the clinical profile of individuals with aphasia. However, with respect to naming and naming recovery, the majority of studies have employed functional MRI (fMRI) to examine patterns of activation associated with naming, and with treatment-induced neural change. These findings are discussed in turn below.

1.1.1 Neural correlates of naming

Naming, which involves speech sound production in response to a visual stimulus, is dependent upon the integration of various cognitive processes (i.e., semantic, phonological, perceptual), and is thus known to activate a widespread network of brain regions corresponding

to these processes (Price et al., 2005). According to current accounts, speech sound representations are processed in the superior temporal gyrus (STG) and mapped onto meaning representations via a ventral route, from the posterior inferior temporal gyrus (ITG), extending to the inferior frontal gyrus (IFG) pars orbitalis; integration with prior linguistic knowledge occurs in the anterior temporal lobe and extends to the pars triangularis and pars opercularis of the IFG (Davis, 2016). Mapping speech sounds to articulatory representations occurs via a dorsal route, in the temporoparietal junction area, with connections to the precentral gyrus (Davis, 2016). This is generally in line with prominent contemporary models of speech and language processing in the brain (e.g., see Hickok & Poeppel, 2004; Hickok & Poeppel, 2007).

Based on findings from a meta-analysis of object naming by Price and colleagues (2005), semantic processing has been associated with activation in bilateral anterior and posterior middle temporal gyrus (MTG), middle occipital cortices and cerebella, and the left angular gyrus, left cuneus and right IFG. The left ITG and STG and left temporal pole have also been implicated in semantic processing during picture naming (Jarret et al., 2022). In addition, lesion-symptom mapping studies have found that semantic processing is mediated by an extended ventral ("sound to meaning") network and can be impaired following damage to the anterior temporal lobe (i.e., temporal pole, anterior MTG and STG; Mirman et al., 2015; Mirman & Thye, 2018). Semantic processing has also been associated with the inferior fronto-occipital and uncinate fasciculi, white matter tracts that connect the frontal lobes to multiple distributed brain regions (Mirman et al., 2015; Mirman & Thye, 2018; Jarret et al., 2022), the inferior longitudinal fasciculus (connecting occipital, inferior temporal and inferior frontal regions), the middle longitudinal fasciculus (connecting parietal and temporal regions) and the extreme capsule (connecting the angular gyri and STG with the ventrolateral prefrontal cortex; Jarret et al., 2022).

Phonological processing and/or speech production has been associated with activation in the left hemisphere frontal operculum, IFG, insula, anterior cingulate, cerebellum and thalamus (see meta-analysis by Price et al., 2005). In addition, the left inferior and superior temporal gyri, precentral gyrus and supplementary motor area have been implicated in phonological processing during picture naming (Jarret et al., 2022). Lesion-symptom mapping studies have demonstrated that phonological processing is mediated by dual pathways, such that lesions to the dorsal ("sound to speech") stream (i.e., supramarginal gyrus - SMG, inferior postcentral gyrus, precentral and premotor cortices) lead to impaired phonological production, and lesions to the ventral stream (i.e., posterior to anterior STG) lead to impaired phonological recognition (Mirman & Thye, 2018; Mirman et al., 2015). Further, phonological processing has

been associated with the arcuate fasciculus (a white matter tract connecting posterior temporal and anterior frontal regions) and the frontal aslant tract (connecting medial- and inferior frontal regions; Jarret et al., 2022).

Finally, auditory processing of spoken responses during picture naming has been associated with activation in bilateral STG and left MTG regions, and perceptual processing of visual stimuli during picture naming has been associated with the right inferior occipital cortex, and the left ventral cuneus, left lingual gyrus and left middle fusiform gyrus (Price et al., 2005).

1.1.2 Neural correlates of treatment-induced anomia recovery

Broadly speaking, recovery of naming after treatment has been associated with increased functional activity in perilesional and spared left hemisphere regions (e.g., Fridriksson et al., 2012; Fridriksson et al., 2006; Leger et al., 2002; Meinzer et al., 2008; Rochon et al., 2010; van Hees et al., 2014b). Other studies have attributed treatment success to increased activity bilaterally (e.g., Abutalebi et al., 2009; Leonard et al., 2015; Marcotte et al., 2018; Menke et al., 2009) or primarily in the right hemisphere (e.g., Della Rosa, et al., 2014; Vitali et al., 2010; Meinzer et al., 2006). On the other hand, evidence also suggests that treatment-related improvements are associated with decreases in activation across both left- and right-hemisphere language regions (e.g., Marcotte et al., 2018; Nardo et al., 2017; Bruehl et al., 2021; Crosson et al., 2009). Finally, some studies have demonstrated a normalization of functional activation and/or connectivity (i.e., becoming more similar to controls) after therapy (Kiran et al., 2015; Kiran et al., 2019; Peck et al., 2004; van Hees et al., 2014c), whereas others have demonstrated increased post-therapy activation relative to controls (e.g., Johnson et al., 2019).

Further, treatment is thought to have broad effects on the brain, as it may stimulate numerous functions and/or processes simultaneously (Turkeltaub, 2019). Studies have reported broad therapy-induced changes in brain activation, both within the language network as well as in regions not traditionally associated with language processing. Neuroscientific frameworks of spontaneous post-stroke language recovery suggest that in damaged language networks, there may be a greater recruitment of residual right-hemisphere lesion homologues, and residual non-linguistic cognitive networks (mediating executive control, memory and learning processes), in order to successfully complete linguistic tasks (Heiss & Thiel, 2006; Saur et al., 2006; Stefaniak et al., 2022; Stockert et al., 2020; Kiran, Meier & Johnson, 2019; Geranmayeh et al., 2017; Geranmayeh et al., 2014; Brownsett et al., 2014). For example, Brownsett and colleagues (2014) found that activation of the dorsal anterior cingulate cortex/superior frontal gyrus (a part

of the domain-general saliency and central executive networks) predicted performance on a picture description task in individuals with post-stroke aphasia.

There is evidence to suggest that these broader brain networks are also recruited in treatment-induced language recovery (see Kiran et al., 2019 and Crinion & Leff, 2015). Studies have documented greater right-hemisphere involvement following therapy, especially in those with larger left-hemisphere lesions (e.g., Tuomiranta et al., 2015; Vitali et al., 2010; Crosson et al., 2009). Likewise, treatment-induced language recovery may involve the recruitment of nonlinguistic cognitive processes, mediated by regions outside of the language network, such as the prefrontal cortices (Abel et al., 2014), the anterior cingulate cortex and left caudate (Abutalebi et al., 2009; van Hees et al., 2014b), the right precuneus (van Hees et al., 2014b), and the hippocampus and surrounding structures (Meinzer et al., 2010; Menke et al., 2009).

In addition, treatments primarily targeting a specific process are also likely to induce neural changes primarily in the brain regions and/or networks supporting that process (Turkeltaub, 2019). For example, melody and rhythm-based approaches to language therapy have been developed to target the intact right hemisphere and there is some evidence to suggest right-hemisphere neural changes associated with these approaches (e.g., Schlaug, Marchina & Norton, 2009). Similarly, some evidence suggests that treatments combining naming with complex left-hand motor movements (also targeting the intact right hemisphere), may lead to increased brain activation in right hemisphere regions (i.e., frontal motor and premotor cortices, e.g., Crosson et al., 2009). Further, one study that administered naming treatment using both semantic and phonological cueing found that a post-treatment reduction in semantic paraphasias was associated with increased activation in residual temporal lobe language network regions (i.e., ventral areas implicated in semantic processing), whereas a post-treatment reduction in phonemic paraphasias was associated with increased activation in residual temporoparietal language network regions (i.e., dorsal structures implicated in phonological processing; Fridriksson et al., 2012). Although these findings are intriguing, further research is needed to determine whether a specific treatment approach consistently induces a specific pattern of neural change. To date, the evidence on this question has produced somewhat inconclusive results (e.g., see Schevenels, et al., 2020).

1.2 Methodological Considerations

Increasingly, researchers are acknowledging the potential for neuroimaging data to inform language rehabilitation research and contribute neuroscientific evidence to complement existing behavioural findings. However, as evidenced above, fMRI activation patterns vary

widely across aphasia and anomia treatment studies and the specific mechanisms underlying treatment-induced neuroplasticity remain somewhat unclear (Hartswigen & Saur, 2019; Kiran et al., 2019). Such variability in findings may reflect the inherent heterogeneity of MRI procedures used across studies, especially when evaluating lesioned brains (Meinzer et al., 2013; Poldrack et al., 2008; Wilson & Schneck, 2020). As a result, the interpretation of MRI findings can vary substantially as a function of the study design, outcome measures, MRI techniques and reporting standards employed (Meinzer et al., 2013; Poldrack et al., 2008; Turkeltaub, 2019; Wilson & Schneck, 2020).

First, fMRI relies on neurovascular coupling to produce a blood-oxygen-level-dependent (BOLD) signal. It is known that neurovascular coupling is variable in healthy adults, and even more so in older, structurally- or vascularly impaired brains (Veldsman et al., 2015), where signal noise can be high (Blank et al., 2017). Thus, selection of significance thresholds can lead to variability in the results observed across studies. In addition, given the large variability in lesion sites associated with naming (and naming deficits), it is important to consider brain regions both within and outside of the language network. This is especially true in damaged brains where activations can arise in new areas as a compensatory mechanism (Blank et al., 2017). Relatedly, when comparing the patterns of activation elicited by a language task in participants with aphasia versus healthy controls, the cognitive load of the tasks used in the scanner may be reflective of upregulation of non-language regions due to the increased cognitive effort required (relative to healthy controls), rather than of treatment-induced change.

Some of these issues may be mitigated in part through the use of whole-brain activation maps which would reveal all relevant treatment-induced activations, and through the replication (and synthesis) of results across multiple studies, using robust statistical analysis methods (e.g., correction for multiple comparisons, etc.). Finally, a more nuanced and explicit understanding of brain-behaviour relationships may be gained through linking neural activation patterns to specific (e.g., naming accuracy), as opposed to broad (e.g., aphasia severity) behavioural outcomes (Turkeltaub, 2019).

Next, the evidence for treatment-induced recovery from anomia comes from both group- and case study designs, which may offer differing and complementary information about the nature of treatment-induced changes observed in post-stroke aphasia (Poldrack et al., 2008). In group study designs, more statistically robust analyses are possible, but important perilesional activations may be lost when variable lesion sites and volumes are averaged across a group of individuals (Blank et al., 2017; Meinzer et al., 2013). In case-study designs, although important perilesional activations are captured, such findings cannot explicitly be correlated with

corresponding behavioural improvements or easily generalized to the larger population; case-series designs, or aggregated single-case data may mitigate this issue (Meinzer et al., 2013). Thus, group and case-level data have their respective strengths and limitations in neuroimaging research; considering both types of study designs may offer important insights into the neural correlates of treatment-induced language recovery, particularly in the context of a literature review (Blank et al., 2017; Meinzer et al., 2013; Poldrack et al., 2008).

1.3 Objectives

The primary aim of this study is to systematically review current evidence addressing the following question: What are the changes in brain structure and/or functional activation pre- to post-anomia treatment in adults with post-stroke aphasia? Considering the existing gaps in the literature, we review the evidence in two stages. First, we summarize and critically appraise the methodological quality of all relevant case- and group study designs, which, as stated above, may yield different but complementary findings (Meinzer et al., 2013). Second, we use this critical appraisal as a guide to extract and synthesize the main results from the current best evidence reporting on changes in brain function and/or structure associated with anomia treatment. To our knowledge, this is the first systematic review to aggregate case- and group-level findings reporting on neural changes associated specifically with anomia therapy, complementing existing reviews evaluating neuroplasticity in post-stroke aphasia recovery more broadly (Schevenels, et al., 2020; Wilson & Schneck, 2020).

2 Methods

The present review adheres to methods recommended by the Cochrane group (Higgins & Green, 2008), and was registered with PROSPERO, the International Prospective Register of Systematic Reviews (protocol registration # CRD42020188916; available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020188916). Study characteristics, treatment and neuroimaging methods from all relevant studies accepted for review were extracted and summarized, as described in Section 2.4 below. However, after critical appraisal, only a subset of these studies was extracted and included in our data synthesis and summary of main results (as described in Section 2.6 below).

2.1 Operational Definitions

As stated above, this review aims to synthesize current best evidence on neural changes pre- to post-anomia treatment in adults with post-stroke aphasia. All accepted studies acquired both pre- and post-treatment neuroimaging data via MRI-based neuroimaging

techniques (i.e., structural, functional, diffusion MRI), corresponding to brain structure, functional activation, lateralization or neural connectivity. Studies employing MEG, PET or SPECT were not accepted. Anomia treatment was defined as any behavioural therapy specifically targeting impairments in naming ability. Thus, treatments that primarily targeted word production and employed naming as a primary outcome measure were accepted, regardless of word class (e.g., nouns, verbs) and treatment modality (e.g., telerehabilitation or face-to-face therapy). Sentence and/or discourse-level treatments, or treatments primarily targeting comprehension or motor speech impairments were not considered for review. In addition, treatments employing electrical stimulation or pharmacological intervention were not considered unless behavioural intervention data from sham and/or placebo conditions were available. Adults were defined as study participants aged 18 years and older. Aphasia was defined as any language production and/or comprehension difficulty (written or spoken) acquired following a cerebrovascular accident or stroke. Studies reporting on developmental and/or progressive language impairments, or aphasia due to other neurological disorders (e.g., tumor, epilepsy, traumatic brain injury) were not accepted for review.

2.2 Search Strategy

We conducted electronic searches of the following databases, from all previous years (as determined by the database) to November 9th, 2022: Cumulative Index of Nursing and Allied Health Literature (CINAHL), Cochrane Trials, Embase, Ovid MEDLINE, MEDLINE-in-Process and PsycINFO. Search strategies were individualized for each database and subject headings were used wherever possible. Portions of search strategies from published systematic reviews were adapted for terms related to “aphasia” and “treatment” (Brady et al., 2016; Simic et al., 2019), and terms related to “magnetic resonance imaging” (Lombardi et al., 2020; Roze et al., 2018). Reference lists from accepted studies were also reviewed to ensure inclusion of all relevant articles. Please see Supplementary Table 1 for the MEDLINE search strategy.

2.3 Study Selection

Two independent raters assessed all abstracts (in round one) and full texts (in round two) according to pre-specified inclusion criteria, listed below. Discrepant ratings were resolved by discussion and consensus between raters, or by third-party arbitration wherever consensus could not be reached. Given the differential advantages of neuroimaging at the group versus individual levels, both group (e.g., randomized control trials, cohort studies), and single-case (e.g., case-control, case-series, case reports) study designs were accepted for review. All studies with a published abstract were accepted for review if they: a) presented original data

(i.e., they were not reviews, book chapters, trial protocols, conference proceedings, opinion statements, practice guidelines, position papers, educational reports, or tutorials), b) reported on adults with post-stroke aphasia, c) administered behavioural treatment for anomia, and d) acquired pre- and post-treatment brain images using MRI techniques (i.e., structural- sMRI, functional- fMRI, diffusion-weighted- dMRI).

When evaluating criterion b) above, we required that at least 90% of participants in group studies were adults with stroke etiology; in case-series studies, we extracted data pertaining to stroke patients only. For criterion c) above, studies combining behavioural treatment with electrical stimulation or pharmaceutical interventions were excluded, unless they presented data from a control condition (i.e., anomia therapy plus electrical stimulation sham or drug placebo group, respectively) and met all other inclusion criteria. Studies employing crossover designs, where the effect of behavioural anomia treatment could not clearly be teased apart from the effects of electrical stimulation, pharmaceutical interventions, or behavioural interventions targeting language impairments other than anomia, were excluded.

2.4 Data Extraction

Qualitative data were extracted from each accepted full-text article, including study characteristics (study design, sample size, participant demographics), treatment characteristics (i.e., treatment type and schedule, naming improvement pre- to post-treatment), and MRI characteristics (in-scanner task, control condition, analysis type). To ensure reliability, a second independent rater extracted the same data from a random subset of 20% of the accepted studies. Given the heterogeneity of methods and study designs used, a formal meta-analysis of neuroimaging data (e.g., using activation likelihood estimation methods) was not possible.

2.5 Critical Appraisal

Cochrane's published evidence grading tool was not applicable to the majority of studies (and study designs) in our review. Critical appraisal of the studies accepted for review was primarily focused on the quality of reporting of neuroimaging methods. However, treatment efficacy (i.e., statistically significant improvements in naming accuracy following therapy) was also taken into consideration. For comprehensive reviews of the efficacy of aphasia and anomia therapy, and corresponding ratings of methodological quality, see Brady et al. 2016 and Sze et al., 2021.

To our knowledge, no standardized tool exists to evaluate the quality of reporting neuroimaging methods, particularly in the post-stroke aphasia population. As a result, we developed a critical appraisal tool to systematically evaluate neuroimaging methodology across

all accepted studies, based on published guidelines and recommendations for reporting in fMRI (Poldrack et al., 2008) and aphasia research (Meinzer et al., 2013). Overall, we established 20 indicators of methodological quality for neuroimaging procedures, across three broad categories. The first category includes four items which evaluate the reported MRI sequence characteristics (e.g., scanner make/model, field strength, TR, TE, voxel size) and whether the same sequence characteristics were used pre- and post-treatment. The second category includes seven items evaluating the reporting of pre-processing steps (e.g., co-registration to anatomical image, spatial and temporal corrections, lesion-masking, and normalization). Careful reporting of sequence characteristics and pre-processing steps ensures that neuroimaging results are replicable, and that subsequent data analysis is reliable. For example, accounting for lesions during the pre-processing stage (i.e., during the normalization/warping process) improves the accuracy of localizing functional activations, and of comparing these activations between patients and controls. The third category includes nine items evaluating the statistical analyses reported across studies (e.g., whole-brain activation maps, corrections for all reported multiple comparisons of voxels), which can serve to indicate the robustness of the findings reported in each study. The final indicator (item 20) logs whether treatment-related improvements in naming accuracy were statistically shown across studies. Please see Appendix A for a detailed description of methodological indicators and scoring procedures. Two independent raters with graduate- and PhD-level training in neuroscience, neuroimaging and anomia rehabilitation assessed the methodological quality of all included studies; discrepant ratings were resolved by discussion and consensus.

2.6 Data extraction of main findings

Our critical appraisal of methodological quality was subsequently used to guide the selection of studies for data synthesis. In task-based fMRI activation studies, we extracted the reported Montreal Neurological Institute (MNI) and/or Talairach coordinates, wherever they were available in study tables or in the text. Studies were included in the data synthesis if they reported MNI coordinates based on whole-brain data (Table 4, methodological indicator 15). Whole-brain (i.e., not ROI) data was the primary focus of the present review to ensure that all relevant activations were captured (even those outside the language network). In addition, only studies that directly compared pre- to post-treatment neural activation patterns were included (Table 4, methodological indicator 18). Further, data from participants (or groups of participants) that did not make significant improvements in naming accuracy pre- to post-treatment (Table 4, methodological indicator 20) were excluded from the data synthesis.

Data representing contrasts of interest were subsequently extracted, namely: significant increases in activation after therapy, and significant increases in activation that correlated with improved naming after therapy (i.e., post- versus pre- treatment contrasts). We also extracted data representing significant decreases in activation after therapy, and significant decreases in activation correlated with naming improvement after therapy (i.e., pre- versus post-treatment contrasts). Talairach coordinates were transformed to MNI using Bioimage Suite (https://bioimagesuiteweb.github.io/webapp/mni2tal.html). All extracted MNI coordinates were cross-checked by a second independent rater, to ensure accuracy.

MNI coordinates were then labelled using The Human Brainnetome Atlas (Fan et al., 2016; http://atlas.brainnetome.org), which parcellates the brain into 246 regions (210 cortical and 36 subcortical) and allowed for a fine-grained whole-brain analysis of the data. This atlas also includes 28 cerebellar regions, for a total of 274 regions. Once labelled, we counted the number of significant activations reported for each region in the atlas. Based on these count data, brain images were created using Glass Brain plotting from Nilearn version 0.10.1 (https://nilearn.github.io/). Finally, count data were synthesized in two ways: 1) by aggregating data from all studies meeting the above-mentioned criteria, and 2) by aggregating data from all eligible studies that also reported corrections for all multiple comparisons (Table 4, methodological indicator 19).

The main findings from studies reporting on changes in lateralization and/or connectivity pre- to post-treatment were also summarized. Lateralization and/or functional connectivity (FC) findings based on task-based fMRI were included in data summaries if they met all the criteria outlined above. Studies reporting pre- to post-treatment changes in FC based on resting-state fMRI (rsFC), and pre- to post-treatment changes in structural connectivity based on dMRI were all summarized, given the small number of articles and heterogeneity of connectivity methods used.

3 Results

3.1 Literature Retrieval

Initial search results yielded 3535 articles in total, and 2481 unique citations after duplicates were removed. Following abstract screening, 2175 articles were excluded based on the criteria listed above. As such, 136 full-text articles were assessed for eligibility, and of those, 93 were further excluded (please see Supplementary Materials for a complete list of excluded full-text articles). Overall, 43 articles were accepted for review. Some articles reported data on the same set of participants using different neuroimaging approaches (e.g., rs-fMRI, dMRI and

event-related fMRI in van Hees et al., 2014a, 2014b and 2014c). In these instances, articles reporting on the same sample were merged and labelled as a single study. In instances where two articles reported data on the same sample using the same neuroimaging method, we selected the most recent and/or comprehensive article as the basis for data extraction and synthesis and used the other articles to supplement the data. Thus, hereafter, we distinguish between the terms 'article' and 'study', such that each study represents findings from a unique patient sample, gleaned from a larger set of published articles. A total of 33 studies (comprised of 43 articles in total) were included in the present review. See Prisma flow diagram in Figure 1 for details. Point to point agreement between two independent raters for the first round of abstract reviews was 97.8% (for accepting or rejecting abstracts), and 90.2% (for reason to accept or reject). Point to point agreement between two independent raters for the second round of full-text reviews was 95.6% (for accepting or rejecting full-text articles), and 87.5% (for reason to accept or reject full-texts).

3.2 Study Characteristics

Of the 33 accepted studies, 12 were group designs (i.e., cohort, cohort-control, and parallel-alternating cohort studies), which employed a pre-post-treatment paradigm and conducted group-level neuroimaging analyses. Cohort sample sizes across group studies ranged from four to 30 participants, with a total N of 161. Approximately 65 (i.e., 40%) of the participants were female. On average, participants were in the chronic stages of recovery (i.e., greater than 6 months post-onset), although two studies also included participants who were four- and five-months post onset (Bruehl et al., 2021; Nardo et al., 2017, respectively). The average months post-onset ranged from 24.4 to 142.8 months across group studies. Aphasia type varied across studies, and aphasia severity was relatively equally distributed when aggregating across studies where these data were reported: namely, mild (n = 26), mild-moderate (n = 8), moderate (n = 29), moderate-severe (n = 16), and severe (n = 30). Six studies were conducted in English, and three each in German and French. Finally, eight out of 12 group studies also included a healthy control group. Please see Table 1 for details.

The remaining 21 studies were single case- or case-control studies, case series, case-control series, or single subject multiple baseline designs, with a total N of 62 participants (21 female, or 33.9%), and a mean age of 57.2 years (SD = 12.3). All but four participants were in the chronic stage of post-stroke recovery (see Abutalebi et al., 2009; Davis et al., 2006; Della Rosa et al., 2014), with an average of 51.8 (SD = 67.2) months post-onset. As in the group studies, aphasia type varied across case studies and aphasia severity was evenly distributed.

Namely, severity of aphasia was reported as follows: mild (n=15), mild-moderate (n=1), moderate (n=19), moderate-severe (n=5) and severe (n=12). Twelve studies were conducted in English, four primarily in Italian, three primarily in German, and two in French. Eight out of 21 studies included comparisons to healthy controls. Please see Table 2 for details.

3.2.1 Treatment Characteristics

A variety of anomia treatment types were administered across studies. Namely, nine studies administered phonological treatment approaches, involving progressive syllabic cueing (Abutalebi et al., 2009; Della Rosa et al., 2014; Vitali et al., 2010), Phonological Components Analysis (PCA; Leonard et al., 2015; Marcotte et al., 2018; Rochon et al., 2010), errorless or error-reducing hierarchical phonological cueing (Fridriksson et al., 2006; Nardo et al., 2017) and articulatory gesture training (Leger et al., 2002). Six studies administered semantic treatment approaches, namely Semantic Feature Analysis (SFA; Kiran et al., 2015; Marcotte et al., 2013; Marcotte & Ansaldo, 2010) or semantic decision-making (Davis et al., 2006; Johnson et al., 2019; Sandberg et al., 2015). In addition, seven studies administered both semantic and phonological cueing treatments in an alternating design (Abel et al., 2014; Bruehl et al., 2021; Fridriksson et al., 2012; Fridriksson et al., 2007; van Hees et al., 2014b), or treatment using both semantic and phonological cueing simultaneously (Marangolo et al., 2009; Menke et al., 2009). The remaining ten studies employed naming plus gesture treatments (Benjamin et al., 2014; Crosson et al., 2009; Durand et al., 2021; Peck et al., 2004), naming-focused Intensive Language-Action Therapy (ILAT; McKinnon et al., 2017), naming-focused Constraint-Induced Aphasia Therapy (CIAT; Kurland et al., 2012; Meinzer et al., 2008; Meinzer et al., 2007; Meinzer et al., 2006), naming-focused Constraint-Induced Language Therapy (CILT; Kurland et al., 2010) and naming-focused Promoting Aphasic's Communicative Effectiveness (PACE) therapy (Kurland et al., 2012; Kurland et al., 2010). Treatment schedules varied widely across studies, whereby session length ranged from 20 minutes to four hours per day, session frequency ranged from two to five days per week, and overall treatment duration ranged from two to 12 weeks. Please see Table 3 for details.

Although studies reported various language outcome measures at post-treatment and follow-up stages, the outcome of primary interest in the present review was naming ability pre- to immediately post-treatment, corresponding with the neuroimaging acquisitions across the majority of studies. Taken together, all studies reported pre- to post-treatment improvements in naming ability, and these improvements were statistically demonstrated in all but five studies

(i.e., Della Rosa et al., 2014; Fridriksson et al., 2006; Marcotte & Ansaldo, 2010; Meinzer et al., 2007; Meinzer et al., 2006). Please see Table 3 and item 20 in Table 4 for details.

3.2.2 MRI Study Characteristics

The imaging method used in the majority of studies (n = 31) was task-based fMRI, with 21 studies employing an event-related design, and 10 studies employing a block design (Table 3). The in-scanner task was overt picture naming in 24 studies, overt category member generation (in 3 studies), overt semantic verification (in 1 study), and overt picture and written rhyme judgment (in 1 study). Four studies employed a covert task in the scanner, including: semantic and rhyme judgments (in 2 studies), concreteness judgments (in 1 study), and lexical decision-making, verb generation and text listening (in 1 study). In addition, three studies also reported resting-state fMRI data (Durand et al., 2021; Masson-Trottier et al., 2021; van Hees et al., 2014c), and three reported structural diffusion imaging data (McKinnon et al., 2017; van Hees et al., 2014a; Braun et al., 2022).

The control task in the scanner varied across studies and included passive viewing of a fixation cross in eight studies (Abel et al., 2014; Benjamin et al., 2014; Bruehl et al., 2021; Crosson et al., 2009; Johnson et al., 2019; Meinzer et al., 2008; Meinzer et al., 2007; Meinzer et al., 2006), passive viewing of abstract and/or scrambled images in four studies (Fridriksson et al., 2012; Fridriksson et al., 2007; Fridriksson et al., 2006; van Hees et al., 2014b), viewing of abstract and/or scrambled images with a verbal response (e.g., “baba” or “pass”) in six studies (Durand et al., 2018; Kiran et al., 2015; Kurland et al., 2012; Kurland et al., 2010; Marcotte et al., 2013; Marcotte et al., 2010), viewing a fixation cross with a button press and judging the size of pictured objects with a button press in two studies (Leonard et al., 2015; Rochon et al., 2010), covert lexical decision in one study (Davis et al., 2006), categorical decision (strings of vowels versus consonants) in one study (Sandberg et al., 2015), picture naming with a noise control cue in one study (Nardo et al., 2017), and rest in one study (Leger et al., 2002). In addition, seven studies did not report an in-scanner control task (Abutalebi et al., 2009; Della Rosa et al., 2014; Marangolo et al., 2009; Marcotte et al., 2018; Menke et al., 2009; Peck et al., 2004; Vitali et al., 2010).

To ascertain reliability, the data from 10 articles (i.e., 23% of total yield) were extracted by a second independent rater. Point-to-point agreement between raters for the extraction of the study, treatment and imaging characteristics described above was 91.8%, indicating excellent reliability.

3.3 Quality of Reporting Neuroimaging Methods

To ensure a thorough evaluation of the studies accepted for review, we assessed the methodological quality of reporting at the article- not study-level. This allowed us to evaluate the methodological quality of reporting for the various imaging approaches used across all articles, including those belonging to the same study. As such, the summaries that follow are based on the 43 articles included in the review. The quality of reporting of each article was assessed by two independent raters; point to point agreement was 88%.

The quality indicators developed for this review fall under three broad categories, evaluating the reporting of: MRI sequence characteristics, pre-processing steps, and statistical analyses (see Appendix A). Detailed scoring for each article is presented in Table 4. Broadly speaking, the quality of reporting neuroimaging procedures was variable (see Figure 2). With respect to MRI sequence characteristics (Figure 2A), reporting was generally of high quality, with 93% of studies reporting acquisition of an anatomical image, 65% reporting all required sequence characteristics for the anatomical image, and 79% reporting all required sequence characteristics for functional or structural images; the same sequence characteristics were used pre- and post-treatment in 86% of studies.

The reporting of pre-processing steps was somewhat more variable (Figure 2B). Namely, 84% of studies reported spatial (i.e., motion) correction, but 58% reported temporal corrections (i.e., slice timing) and 55% reported co-registration to the anatomical image. In studies with group-level neuroimaging data and/or with comparisons to healthy controls, 87% reported normalization to MNI or Talairach templates during pre-processing, and 68% reported spatial smoothing. In addition, approximately 47% of studies reported lesion-masking during normalization, which is an important pre-processing step as it improves the accuracy of localizing functional activations, and of comparing these activations with healthy control groups. Of the three studies reporting diffusion imaging data, one study (van Hees et al., 2014a) used more than one direction per voxel to reconstruct fiber tracts, whereas the other studies did not (McKinnon et al., 2017; Braun et al., 2022).

Finally, the reporting of statistical analyses across studies was also somewhat variable (see Figure 2C). Importantly, 79% of studies reported direct statistical comparisons pre- to post-treatment, which was the comparison of primary interest in the present study. In addition, 76% of studies reported fMRI BOLD activation patterns based on whole-brain (as opposed to ROI) analyses. In event-related fMRI designs, 65% of studies specified whether incorrect naming events were included in the analysis, and 54% reported the number of correct and incorrect naming events. Among the six studies that calculated laterality indices (LIs), two based those

calculations on whole-brain functional activation patterns, and all six described and/or depicted the regions of activation pre- to post-treatment; that is, LI calculations were based on activations pertinent to language processing. Notably, only 37% of studies reported corrections for all multiple comparisons of voxels, and 10% of studies reported acquisition of repeated baseline scans. As mentioned above, all but five studies (i.e., 88%) demonstrated statistically significant improvements in naming pre- to post-treatment.

3.4 Data Synthesis: summary of main results

The appraisal of methodological quality was used as a guide to determine which results to include in our data summary. Among the fMRI activation studies (n=31), seven were excluded because they did not employ whole-brain data analyses (Table 4, methodological indicator 15), and nine were excluded because they did not directly compare pre- to post-treatment neural activation patterns (Table 4, methodological indicator 18). Of the remaining 15 studies, four did not demonstrate statistically significant improvements in naming pre- to post-treatment and were also excluded (Della Rosa et al., 2014; Fridriksson et al., 2006; Meinzer et al., 2007; Meinzer et al., 2006). Thus, a total of 11 studies were deemed eligible for data synthesis. Six studies presented group-level neuroimaging data (Abel et al., 2014; Abel et al., 2015; Bruehl et al., 2021; Fridriksson et al., 2010; Menke et al., 2009; Sandberg et al., 2015; van Hees et al., 2014b), and six studies presented case-level neuroimaging data (Fridriksson et al., 2007; Kurland et al., 2012; Leger et al., 2002; Marangolo et al., 2009; Marcotte et al., 2018; van Hees et al., 2014b). We removed activations corresponding to individual participants that did not show significant improvements in naming following treatment (e.g., one out of two cases in Marcotte et al., 2018). Finally, of the 11 studies selected for data synthesis, seven reported corrections for all multiple comparisons of voxels (Table 4, methodological indicator 19). Therefore, the data summaries that follow are presented for a) all 11 studies selected for data synthesis, and b) the seven studies that also reported corrections for multiple comparisons (Abel et al., 2015; Bruehl et al., 2021; Fridriksson et al., 2010; Fridriksson et al., 2007; Kurland et al., 2012; Marangolo et al., 2009; van Hees et al., 2014b). Results from the studies excluded for the various reasons listed above are summarized narratively in Supplementary Table 2.

Of the eleven selected studies, two additionally used task-based fMRI data to report changes in lateralization (Kurland et al., 2012) and FC (Sandberg et al., 2015). Three studies reported pre-to post-treatment changes in FC based on resting-state fMRI (Durand et al., 2021; Masson-Trottier et al., 2021; van Hees et al., 2014c), and three studies reported pre- to post-

treatment changes in structural connectivity based on dMRI (Braun et al., 2022; McKinnon et al., 2017; van Hees et al., 2014a). These findings are summarized in turn below.

3.4.1 Summary of fMRI activation results

Of primary interest were regions demonstrating significant increases in activation following therapy (i.e., post- versus pre-treatment contrasts) that were correlated with behavioural naming improvement, as well as regions demonstrating significant increases in activation following therapy without explicit correlations to naming ability (Figure 3). We also synthesized regions demonstrating significant decreases in activation following therapy (i.e., pre- versus post-treatment contrasts) that were correlated with behavioural naming improvement, and regions demonstrating significant decreases in activation post-therapy without explicit correlations to naming ability (Figure 4). These findings are discussed in turn below.

3.4.1.1 Significant pre- to post-treatment increases in activation correlated with naming improvement.

Two group studies (total N of 27), administering alternating (Fridriksson et al., 2010) or combined (Menke et al., 2009) semantic and phonological therapy, reported significantly activated regions post- versus pre-treatment that correlated with behavioural naming outcomes. Overt picture naming was the in-scanner task in both studies. One study used passive viewing of abstract images as the control task in the scanner, and reported corrections for multiple comparisons (Fridriksson et al., 2010). The other study did not report an in-scanner control task, nor corrections for multiple comparisons (Menke et al., 2009). Please see Table 5 for a summary of all reported activations. Regions showing increased pre- to post-treatment activation associated with naming improvements were primarily in the left hemisphere frontal and parietal lobes. Namely, the left inferior frontal junction, and the left rostral inferior parietal lobule (IPL), that is, the SMG. These findings hold after eliminating activations that were not corrected for multiple comparisons (Figure 3c). No case-series design studies correlated post- versus pre-treatment activation changes with behavioural outcomes.

3.4.1.2 Significant pre- to post-treatment increases in activation

The post- versus pre-treatment contrast represents regions in which activation significantly increased following therapy. Two group studies (total N of 23) reported regions of significant activation for post versus pre-contrasts after alternating semantic and phonological (Abel et al., 2014) or semantic (Sandberg et al., 2015) treatment approaches. The in-scanner

tasks for these studies were naming versus passive viewing of a fixation cross (Abel et al., 2014) and covert concreteness judgments versus categorical decisions (vowel or consonant letter strings) with a button press (Sandberg et al., 2015). Significant increases in activation pre- to post-treatment were primarily reported in the left medial superior frontal gyrus (SFG), left STG, rostral areas of the left IPL (i.e., SMG), the left precuneus and the left thalamus. Additionally, activations were noted in the right hemisphere rostral IPL, right postcentral gyrus and right dorsal caudate. All reported regions of activation are summarized in Figure 3b (and Table 5); note that neither study corrected for multiple comparisons, thus there is no column in Table 5 for this contrast.

In addition, significant peak activations for post- versus pre-treatment naming contrasts were reported in 14 cases, across six single-case/case-series design studies (Fridriksson et al., 2007; Kurland et al., 2012; Leger et al., 2002; Marangolo et al., 2009; Marcotte et al., 2018; van Hees et al., 2014b). In all studies, overt picture naming was the in-scanner task. This was contrasted with passive viewing of abstract and/or scrambled images in two studies (Fridriksson et al., 2007; van Hees et al., 2014b), viewing of abstract images with a verbal “pass” response in one study (Kurland et al., 2012), and rest in one study (Leger et al.,2002). Two studies did not report a control task in the scanner (Marangolo et al., 2009; Marcotte et al., 2018). All but two studies corrected for multiple comparisons (Marcotte et al., 2018; Leger et al., 2002). Regions of increased activation post- compared to pre-treatment were primarily in the bilateral parietal lobes, namely the precunei, IPLs, and to a somewhat lesser extent, the superior parietal lobes (SPLs) and postcentral gyri. Activations were also reported in the bilateral hippocampi and cingulate gyri, as well as the bilateral frontal lobes (i.e., medial and dorsolateral SFG and orbitofrontal gyri - OFG). Bilateral activations (albeit more so in the left hemisphere) were also noted in the fusiform gyri of the temporal lobe, and the basal ganglia (dorsal caudate and putamen). Additional activations were reported in the left middle frontal gyrus (MFG) and left IFG, the left precentral gyrus, the left MTG, left insula, and left thalamus. Occipital lobe activations were reported in the left lateral- and right medioventral cortex and right medial superior occipital gyrus, and in cerebellar lobules (bilateral crus II, left VI and right VIIIa). These results remain largely unchanged when removing activations that were not corrected for multiple comparisons. All reported regions of activation for case studies with post- versus pre-treatment contrasts are summarized in Table 5, Figure 3a.

Based on the available data, we were also able to stratify the case-level post- versus pre-treatment contrasts by treatment type. The following summaries include only data from studies that reported multiple comparison corrections. For phonological treatment approaches,

post- versus pre-treatment activations were available in 8 cases across two studies (Fridriksson et al., 2007; van Hees et al., 2014b). Reported regions of increased activation following phonological therapy were primarily in the left IPL and left precuneus, as well as the bilateral fusiform gyri. For CILT and/or PACE treatments, post- versus pre-treatment activations were available in 2 cases from one study (Kurland et al., 2012). In this study, increased activations were noted primarily in the right parietal lobe (SPL, IPL, precuneus), the bilateral postcentral gyri, the left dorsolateral and medial SFG, left cingulate gyrus and the left dorsal caudate. For semantic therapy, post- versus pre-treatment activations were available in 7 cases from one study (van Hees et al., 2014b). Increased activation was most commonly reported in the left precuneus. However, given the small number of studies, these findings must be interpreted with caution.

3.4.1.3 Significant decreases in pre- to post-treatment activation correlated with naming improvement.

Two group studies (total N of 26), administering alternating semantic and phonological cueing treatments (Abel et al., 2014; Bruehl et al., 2021) reported decreases in activation pre- to post-treatment that correlated with behavioural naming improvements; one of these studies corrected for multiple comparisons (Bruehl et al., 2021). In both studies, the in-scanner task was overt picture naming contrasted with passive viewing of a fixation cross. Regions showing decreased pre- to post-treatment activation associated with naming improvements were primarily in the left hemisphere parietal and occipital lobes, namely, the left rostral IPL (i.e., SMG), the left precuneus, the left lateral occipital cortex and the right medioventral occipital cortex. When removing activations that were not corrected for multiple comparisons, regions showing decreased pre- to post-treatment activation associated with naming improvements were mainly circumscribed to the right medioventral occipital cortex and left precuneus. Please see Figure 4c, and Table 6 for details.

3.4.1.4 Significant pre- to post-treatment decreases in activation

Two group studies (total N of 26), administering semantic and/or phonological therapy (Abel et al., 2015; Bruehl et al., 2021) reported pre- versus post-treatment contrasts representing regions in which activation decreased after therapy. In both studies, the in-scanner task was overt picture naming contrasted with passive viewing of a fixation cross. Both studies corrected for multiple comparisons. Significant decreases in activation were reported in the bilateral cingulate gyri, the left inferior frontal junction of the MFG, left precentral gyrus, left paracentral lobule, left SPL and left cerebellar VI lobule. Significant decreases in activation

following therapy were also noted in the right fusiform, right precuneus and right lateral occipital cortex (see Figure 4b and Table 6).

In addition, significant activations for pre- versus post-treatment contrasts were reported in 8 cases, across 4 single-case/case-series studies (Leger et al., 2002; Marangolo et al., 2009; Marcotte et al., 2018; van Hees et al., 2014b), representing regions in which activation decreased after semantic and/or phonological therapy. Two studies corrected for multiple comparisons (Marangolo et al., 2009; van Hees et al., 2014b). In all studies, overt picture naming was the in-scanner task. This was contrasted with passive viewing of abstract and/or scrambled images (van Hees et al., 2014b), and rest (Leger et al.,2002); two studies did not report a control task in the scanner (Marangolo et al., 2009; Marcotte et al., 2018). Significant decreases in activation pre- to post-treatment were reported in bilateral STG, MTG, cingulate gyri, and medioventral occipital cortices, and in the left medial SFG, left precentral gyrus, left posterior parahippocampal gyrus, and left IPL (SMG and angular gyri). Additional decreases in activation were reported in the right ventral MFG, right ventral IFG, and right precuneus. These results remain largely unchanged when removing activations that were not corrected for multiple comparisons. Please see Figure 4a and Table 6.

3.4.2 Summary of lateralization and connectivity results

Among the eleven task-based fMRI studies accepted for review after critical appraisal, two studies additionally reported laterality or bilaterality indices based on the ratio of task-based fMRI activation (Kurland et al., 2012) or FC (Sandberg et al., 2015) in the left versus the right hemispheres. In addition, two studies used task-based fMRI to report FC based on joint independent components analysis (Abel et al., 2015), and node degree calculations within functional ROIs (Sandberg et al., 2015). Three studies reported FC measures based on resting-state fMRI (Durand et al., 2021; Masson-Trottier et al., 2021; van Hees et al., 2014c), and three studies used diffusion-weighted MRI to report structural connectivity metrics (i.e., mean kurtosis, fractional anisotropy, mean diffusivity; Braun et al., 2022; McKinnon et al., 2017; van Hees et al., 2014a). These findings are summarized below.

3.4.2.1 Lateralization findings

Kurland et al., 2012 administered CILT and PACE treatments, and found predominant right lateralization post-treatment compared to baseline for one participant and predominant left lateralization post-treatment for another. In addition, correct naming recruited primarily left lateralized (perilesional) cortex, whereas incorrect naming recruited primarily right lateralized cortex. Further, after a semantic treatment for anomia, Sandberg and colleagues (2015) found

that individuals showed greater within- versus cross-hemisphere changes in FC. Treatment success was associated with left-lateralized increases in FC, whereas poor generalization was associated with right-lateralized changes in connectivity.

3.4.2.2 Connectivity findings

With respect to FC, the left IFG emerged as an important region associated with treatment-induced change. For example, Sandberg and colleagues (2015) found that individuals who responded to semantic treatment (i.e., improved naming of abstract words) most commonly showed increased FC in the left IFG triangularis; individuals who showed treatment generalization (i.e., improved naming of concrete words) most commonly showed increased FC in the left medial SFG and right IFG triangularis. In addition, disconnection of the left IFG was associated with poorer treatment gains after alternating semantic and phonological cueing treatments (Abel et al., 2015). It appears that large lesions of the left IFG disconnect not only anterior and posterior language areas but may also disrupt the activation of right hemisphere lesion homologues as a compensatory mechanism (Abel et al., 2015).

With respect to rsFC, individuals with aphasia demonstrated upregulation and normalization of rsFC in the language network (relative to controls) particularly in the left hemisphere, following alternating semantic and phonological cueing therapies (van Hees et al., 2014c). Greater rsFC in the left MTG, left SMG and right IFG pars triangularis was significantly correlated with naming improvements after PCA (a phonological cueing treatment; van Hees et al., 2014c). Similarly, another study found increased rsFC in the left-hemisphere post-treatment (and decreased rsFC in the right hemisphere; Masson-Trottier et al., 2021). However, in this study, no correlations were found between improvements in naming after PCA and rsFC changes (Masson-Trottier et al., 2021). After a combined naming and movement therapy (i.e., verb naming with gesture and visualization), increased rsFC was observed between the right IFG and the left thalamus (relative to controls), and in regions associated with visuo-motor, language and action processing (i.e., right cuneus to left supracalcarine gyrus; right precentral gyrus to left lingual gyrus; right parahippocampal to left SPL). The authors suggest that these changes reflect network-level integration of visual and sensorimotor systems after therapy (Durand et al., 2021).

With respect to structural connectivity based on dMRI, the left inferior longitudinal fasciculus (ILF) emerged as an important ventral white matter fiber tract related to treatment-induced improvements in naming accuracy. Namely, studies reported significant increases in FA of the left ILF following semantic therapy (Braun et al., 2022), and significant increases in mean

kurtosis of perilesional left ILF following constraint induced ILAT (McKinnon et al., 2017). Further, this increase in mean kurtosis in the L ILF was strongly correlated with a decrease in semantic paraphasias (McKinnon et al., 2017). In addition, one study found increases in the mean generalized FA of the left arcuate fasciculus following alternating semantic and phonological cueing treatments (interpreted by the authors as improved white matter fiber integrity); pre- and post-treatment generalized FA measures of the left arcuate fasciculus were correlated with long-term maintenance of words treated using PCA (van Hees et al., 2014a). Finally, two studies suggest that treatment may contribute to upregulation and normalization of diffusion measures (as compared to controls) in the left ILF (McKinnon et al., 2017) and the left AF (van Hees et al., 2014a).

4 Discussion

To our knowledge, this is the first systematic review to appraise and synthesize the existing MRI-based evidence pertaining to changes in brain structure and/or function specifically following anomia treatment in adults with post-stroke aphasia. The first stage of review involved aggregating and critically appraising the methodological quality of all relevant studies on this topic. Acknowledging the strengths and drawbacks of each, we accepted both case- and group-study designs in order to obtain complementary neuroimaging findings on treatment-induced recovery of a specific behavioural outcome measure, that is, naming ability (Blank et al., 2017; Meinzer et al., 2013; Poldrack et al., 2008; Turkeltaub, 2019). At the second stage, our critical appraisal was used as a guide to select the best available evidence for more detailed synthesis of results, which summarizes the findings from studies directly comparing pre- to post-treatment whole-brain activations. Data pertaining to changes in lateralization or connectivity associated with naming treatment were also synthesized.

The overwhelming majority of studies reported BOLD peak activation data based on task-based fMRI. Data pertaining to changes in FC were available to a lesser degree and the current evidence base is somewhat limited in terms of the structural changes that may occur following anomia treatment. A variety of anomia treatment approaches were used across studies, and most provided measures of naming improvement following treatment. Importantly, however, only four studies directly correlated these naming improvements with changes in whole-brain functional activation pre- to post-treatment (Fridriksson et al., 2010; Menke et al., 2009; Abel et al., 2014; Bruehl et al., 2021). Overall, the studies reviewed highlight the heterogeneity of MRI approaches employed and the relative paucity of robust findings on this topic in the existing literature. Below, we discuss the findings from this review with respect to

study design and methodological quality. Although limited by the small number of studies in our data synthesis, we also discuss patterns in fMRI activations and structural- and functional connectivity that may be associated with treatment-induced anomia recovery.

4.1 Study design

The present review accepted articles presenting both case- and group-level analyses of neuroimaging data, in order to capitalize on the relative strengths of each type of study design (Blank et al., 2017; Meinzer et al., 2013). Roughly 60% of the studies reviewed were single case or case-series designs. Although less generalizable, case-level analyses may allow for more nuanced detection of activation in perilesional (left-hemisphere) brain areas. On the other hand, group-level analyses enable direct correlations with behavioural improvements but may overrepresent right hemisphere activations when variable lesion sites and volumes are averaged across a group of individuals.

As such, we expected to see a greater number of right versus left hemisphere activations in group-level data, and equal or greater left versus right hemisphere activations in case-level data. However, this prediction was not borne out in our data synthesis: case- and group-level data showed similar levels of activation in the left versus right hemispheres. What did emerge in our data synthesis is that significant increases in activation following treatment were more often reported in the left, compared to the right hemisphere in both case- and group-level data; significant decreases in activation following treatment were reported with relatively equal frequency bilaterally in both case- and group-level data (see hemisphere totals in Tables 5 and 6). Although speculative and requiring further empirical study, this trend in the data suggests that treatment may improve the efficiency of neural processing both by increasing activity in left-hemisphere language regions and by decreasing bilateral activations that may be inefficient or maladaptive. It may also be that longitudinal whole-brain measures of neural *change* (pre- versus post- and post- versus pre-treatment) are less susceptible to bias toward the right hemisphere, even in group studies, as compared to single-timepoint measures of peak activation (e.g., pre only, post only).

4.2 Methodological Quality Considerations

This review presents a careful evaluation of the quality of reporting for neuroimaging procedures. While MRI sequence characteristics (e.g., scanner make and strength, slice thickness, voxel size) were reported in adequate detail across studies, the reporting of certain pre-processing steps was less clear. For example, co-registration of anatomical and functional images was reported in about half of eligible studies, despite most of these studies reporting

acquisition of both anatomical and functional images. In addition, lesion masking during the normalization process was reported in less than half of eligible studies. While it may be the case that some of these methodological steps were indeed carried out, they were not reported. Careful and transparent reporting of these steps in future studies is imperative for an adequate interpretation and replication of findings.

With respect to statistical analyses, 79% of studies reported pre- to post-treatment changes in activation and 76% of studies reported activation patterns based on whole-brain data. Notably, less than 40% of studies reported corrections for multiple comparisons. This did not appear to significantly impact our data synthesis, when comparing activations that were and were not corrected. However, this is likely due to the very limited number of studies eligible for review. Clear guidelines with respect to the analysis and reporting of neuroimaging data in aphasia rehabilitation research would be of great benefit in moving research in this field forward. Despite a relatively large yield of studies overall (n=33), very few met and/or reported the necessary methodological criteria to be included in our summary of neuroimaging findings. Fewer still correlated pre- to post-treatment neural changes with behavioural naming improvements. As a result, only tentative statements can be made regarding patterns of brain activation and connectivity associated with treatment-induced naming recovery. Prior reviews of the literature make similar conclusions (e.g., Wilson et al., 2020). Nevertheless, the main findings are summarized below.

4.3 Treatment-induced changes in brain activation

4.3.1 Evidence from task-based fMRI data

Increases in activation following anomia treatment were noted in various brain regions both within and outside of language (and naming) network. Broadly speaking, increases in activation across studies were primarily noted in the parietal and (to a somewhat lesser extent) frontal lobes. Of note, the left rostral IPL (i.e., SMG) consistently demonstrated increased activation in both case- and group-level data and was also correlated with behavioural naming improvements. The IPL forms part of the dorsal speech processing stream, implicated in auditory-motor integration, phonological production, mapping semantic representations onto word form representations (DeLeon et al., 2007; Friederici, 2011; Saur et al., 2008), selection of articulatory gestures (Tremblay & Gracco, 2010), verbal working memory, and phonological short-term memory (Ravizza et al., 2004). This finding suggests that treatment for naming (i.e., word production) deficits targets the dorsal “sound to speech” stream.

However, findings also suggest that anomia treatment may activate regions beyond the language (and naming) network. Of note, significant increases in activation following therapy were also seen in the left precuneus in group-level data, and in bilateral precunei in case-level data. The precuneus has been implicated in episodic memory, reflective self-awareness and consciousness (e.g., Cavanna & Trimble, 2006), and has also been linked to the default-mode network (e.g., Cunningham et al., 2017). Therefore, although not typically associated with the language network, the precuenus may play an important role in anomia rehabilitation in post-stroke aphasia. Aggregate case-level data also revealed pre- to post-treatment activation increase in bilateral SPL and IPL, and bilateral SFG. Temporal lobe activations were primarily reported in the left STG in group studies, and the bilateral fusiform gyri (implicated in auditory comprehension, phonological, lexical and semantic processing; DeLeon et al., 2007; Forseth et al., 2018) in case studies. Additional case-level increases in activation were reported in the bilateral cingulate gyri, left basal ganglia, and left lateral occipital cortex. However, these conclusions must be interpreted with caution, and consideration of the variability of control tasks used in the scanner across studies. Further, based on the limited available data, no strong trends emerged to suggest unique activation patterns as a function of treatment type.

Although much less frequent, decreases in activation following anomia treatment were noted primarily in the bilateral STG and right MFG in case-level data, and the right precuneus, left SPL and left inferor frontal junction in group-level data. Decreased activation in the right medioventral occipital cortex was correlated with naming improvements after therapy. Overall, the findings suggest that anomia therapy primarily leads to increases (versus decreases) in brain activation in regions that closely align with the neural correlates of naming, as well as regions outside of the naming network.

4.3.2 Evidence from functional and structural connectivity data

Relative to fMRI activation studies, a limited number of studies reported on pre- to post-treatment changes in FC, and fewer still reported changes in structural connectivity. However, behavioural improvements in naming were more frequently associated with neural change in studies reporting measures of structural and functional connectivity. Overall, these studies found that pre- to post-treatment improvements in naming ability after semantic and/or phonological therapy for anomia were predominantly associated with increased connectivity of left hemisphere ROIs and perilesional areas within the language (naming) network (Abel et al., 2015; Abutalebi et al., 2009; Kiran et al., 2015; Sandberg et al., 2015; van Hees et al., 2014c). Two studies using diffusion MRI also reported microstructural improvements in perilesional

portions of the left inferior longitudinal fasciculus (i.e., within the ventral stream; McKinnon et al., 2017), as well as the left arcuate fasciculus (i.e., within the dorsal stream; van Hees et al., 2014a), which were significantly correlated with reduced semantic paraphasias, and improved naming ability, respectively. In addition, one study reported poorer treatment gains associated with disconnection of the left IFG, and the authors suggest that this disconnection limited communication not only between anterior and posterior left-hemisphere language areas, but also with right hemisphere homologues (Abel et al., 2015). Studies also reported pre- to post-treatment normalization of connectivity, whereby participants became equivalent or more similar to controls (McKinnon et al., 2017; van Hees et al., 2014a, 2014c), as well as up-regulation and/or compensation of connectivity relative to controls (e.g., in perilesional and/or contralesional areas; Abel et al., 2015; Durand et al., 2021; van Hees et al., 2014a, 2014c).

Connectivity data were primarily reported in studies published in more recent years, suggesting that both functional- and structural connectivity measures are increasingly being used in aphasia treatment research. This trend is in line with suggestions made in recent reviews that investigating the broader connectivity of brain networks may be more favorable than emphasizing activation levels in specific brain regions (e.g., increase, decrease, right, left; Crinion & Leff, 2015; Hartswigen & Saur, 2019; Kiran et al., 2019). However, the connectivity analyses employed were variable, which made it difficult to develop indicators of methodological quality that would be applicable across studies. With additional research, a consensus may be reached as to the essential elements required in a high-quality connectivity analysis in the rehabilitation of post-stroke aphasia.

4.4 Limitations

Despite the relatively large overall yield of studies in this review, the present findings are limited by the relatively small number of studies reporting robust statistical analyses of neuroimaging findings and the even smaller number of studies demonstrating direct statistical relationships between brain and behaviour. Given the small sample, the findings from this review must be interpreted with caution. Furthermore, although studies were carefully selected for data synthesis based on critical appraisal of methodological quality, our findings may nevertheless be somewhat limited by the inclusion of studies using variable in-scanner control tasks (to contrast with overt picture naming), and studies with variable reporting of pre-processing steps, such as co-registration of anatomical and functional images. Further, pre- to post-treatment comparisons of fMRI data may be unreliable without the use of repeated baseline scans to obtain a more robust statistical picture of baseline neurological activation. In

the present review, only 10% of studies acquired repeated baseline scans to mitigate this issue. In addition, given the heterogeneity of connectivity methods used, our critical appraisal of methodological quality did not include indicators related to network connectivity analyses. Finally, we believe that the criteria used for selecting studies to include in our data synthesis were appropriate to the review question. However, other researchers may disagree. In order to allow for re-analysis and/or re-interpretation of our findings using different criteria, we have included detailed summaries of all relevant studies in this review (Tables 1 to 4 and Supplementary Table 2).

4.5 Conclusions

Taken together, our findings highlight the heterogeneity of MRI procedures and results in the literature, and the relative paucity of robust evidence demonstrating neural change induced by anomia therapy in post-stroke aphasia. Although limited, our findings support the assertion that anomia treatment can activate mechanisms of neuroplasticity in stroke survivors, with the left SMG and left/bilateral precunei emerging as commonly reported regions of treatment-induced change. Further research on the role of these regions in post-stroke anomia rehabilitation is warranted. It was not possible to document reliable treatment-specific neural change based on the current, somewhat limited data set. Thus, it remains unclear, based on current best evidence, whether specific treatments for anomia consistently target specific brain areas corresponding to the cognitive processes being trained. Future research on treatment-induced aphasia recovery must make direct links between neural- and behavioural changes, and would benefit from the use of standardized MRI analysis and reporting procedures in order to improve the interpretability of findings. Additional research is needed on structural changes associated with anomia rehabilitation, and quality indicators must be developed for analyses of structural and functional network connectivity, as these methods are increasingly being used in post-stroke aphasia rehabilitation research.

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Disclosure of Interest

The authors report no conflicts of interest.

Author Note

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Table 1. Characteristics of group studies.

Study	Study Design	N	Age	Sex	Education (yrs)	Handedness	Language	Etiology	Months Post-Onset	Aphasia Type	Aphasia Severity	HC Group
Abel, et al., 2014 *[merge with Abel, et al., 2015]*	Parallel alternating cohort-control	14	35-74 [M = 51.1; SD = 11.6] **	F (4) *M* (10)	9-13 years [M = 10.8; SD = 1.8]	R	German	L CVA ischemic (11) hemorrhagic (2) ischemic + hemorrhage (1)	11-72 [M = 39.1; SD = 17.4]	Broca's (8) Wernicke's (3) Fluent NC (1) TC Sensory (1) Global (1)	NR; at least moderate anomia	14 HC (4 F; 10 *M*) Age 34-73 (median = 48.0; M, SD NR); R-handed Education NR
Benjamin, et al., 2014	Parallel cohorts	7 IT	Range NR [M = 72.1; SD = 10.5]	F (5) *M* (2)	Range NR [M = 14.9; SD = 2.5]	R	English	L CVA ischemic (5) hemorrhagic (2)	12-87 [M = 37.4; SD = 33.5]	Conduction (4) Broca's (2) Anomic (1)	Moderate [WAB-AQ M = 65.5, SD = 8.3]	NA
		7 CT	Range NR [M = 63.0; SD = 9.2]	F (1) *M* (6)	Range NR [M = 12.9; SD = 1.1]	R	English	L CVA ischemic (6) hemorrhagic (1)	10-112 [M = 38.1; SD = 37.4]	Anomic (4) Broca's (1) TC Motor (1) Conduction (1)	Mild-Moderate [WAB-AQ M = 71.9, SD = 11.8]	
Bruehl et al., 2021	Parallel alternating cohort-control	12	21-63 [M = 47.5; SD = 13.8]	F (4) *M* (8)	9-13 years [M = 12.0; SD = 1.7]	R	German	L CVA ischemic (10) hemorrhagic (1) ischemic + hemorrhage (1)	4-61 [M = 24.4; SD = 16.6]	Broca's (7) Wernicke's (2) Global (1) Anomiic (1) Fluent NC (1)	NR; at least mild anomia	22 HC (10 F; 12 *M*) Age (M = 52; SD NR); R-handed Education (M = 12, SD NR)
Durand, et al., 2021 *[merge with Durand et al., 2018]*	Cohort-control	4	59-72 M = 67.0 SD = 6.3	F (2) *M* (2)	8-18 years [M = 12.3; SD = 4.2]	R	French	L CVA ischemic (4)	23-408 [M = 142.8; median = 70; SD = 178.6]	TC Motor (3) Broca's (1)	BDAE 4 - Mild (1) BDAE 3 - Moderate (1) BDAE 2 - Moderate-severe (2) *[based on reported BDAE scale score]*	4 HC (2 F; 2 M) Age: 63-72 (M = 66.0; SD = 4.2); Education: 8-12 (M = 11.8; SD = 3.3); R-handed
Fridriksson, et al., 2012 *[merge with Fridriksson, et al., 2010]*	Parallel alternating cohorts	30*	33-81 M = 59.2 SD = 11.5	F (16) *M* (14)	NR	NR	English	L CVA	6-350 [M = 51.1; SD = 78.3]	Broca's (13) Anomic (10) Conduction (3) Wernicke's (2) TC Motor (1) Global (1)	Mild (10) Moderate (7) Severe (12) Very severe (1)	14 HC (sex NR) Age 26-77 (M, SD NR); R-handed Education NR
Johnson, et al., 2019 *[merge with Johnson et al., 2021; Braun et al., 2022]*	Cohort-control	26 (Tx)	42 - 80 M = 62.8 SD = 10.2	F (9) *M* (17)	NR	R (24) L (2)	English	L CVA	12 - 170 [M = 58.3; SD = 51.8]	NR	Mild (8) Moderate (9) Severe (9) [WAB-AQ M = 60.1; SD = 24.0]	17 HC (6 F; 11 M) Age (M = 60.4; SD = 10.8); R-handed Education NR
		10 (UnTx)	39 - 79 M = 59.0 SD = 11.8	F (0) *M* (10)	NR	R (8) L (2)	English	L CVA	10 - 164 [M = 85.2; SD = 141.9]	NR	Mild (5) Moderate (2) Severe (3) [WAB-AQ M = 65.8; SD = 24.6]	

Marcotte, et al., 2013; *[merge with Marcotte, et al., 2012]*	Cohort-control	9	50-67 M = 62.3 SD = 6.0	F (4) *M* (5)	12-22 [M = 14.9; SD = 3.9]	R	French	L CVA	50-300 [M = 110.2; SD = 92.5]	Broca's (8) Wernicke's (1)	Moderate (1) Moderate-severe (4) Severe (4)	10 HC (6 F; 4 *M*) Age: 66 - 80 [M = 70.2; SD = 4.0] Education 12 - 22 [M = 16.4; SD = 3.8]; R-handed
Masson-Trottier, et al., 2021	Cohort	10	48-82 [M = 68.9; SD = 10.2]	F (3) *M* (7)	8-20 [M = 14.7; SD = 3.4]	R	French	L CVA ischemic (10)	11-172 [M = 43.3; median = 30.0; SD = 48.0]	Anomic (3) Broca's (2) Global (2) TC Motor (2) TC Mixed (1)	BDAE 4 - Mild (2) BDAE 3 - Moderate (2) BDAE 2 - Moderate-Severe (4) BDAE 1 - Severe (2) *[based on reported BDAE scale score]*	NA
McKinnon, et al., 2017	Cohort	8	Range NR [M = 52.0; SD = 7]	F (3) *M* (5)	NR	R	English	L CVA	Range NR [M = 50.3; SD = 29.8]	NR	NR	NA
Menke, et al., 2009	Cohort-control	8	34-67 M = 49.9 SD = 9.9	F (3) *M* (5)	NR	R	German	L CVA ischemic (7) hemorrhagic (1)	22-83 [M = 59.5; SD = 18.0]	Broca's (7) Global (1)	Moderate-severe (6) Severe (2)	9 HC (3 F; 6 *M*) Age: 36-64 (M and SD NR); R-handed Education NR
Nardo, et al., 2017	Cohort	18	21-67 M = 50.4 SD = 11.5	F (6) *M* (12)	NR	R	English	L CVA	5-264 [M = 61.3; SD = 58.2]	NR	NR	NA
van Hees, et al., 2014a *[merge with van Hees et al., 2014b; van Hees et al., 2014c]*	Parallel alternating cohort-control	8	41-69 M = 56.83 SD = 9.15	F (5) *M* (3)	10-16 [M = 12.0; SD = 2.4] **	R	English	L CVA	17-170 [M = 52.3; SD = 49.8]	Anomic (6) Conduction (2)	Mild (5) Mild-Moderate (1) Moderate (2) [WAB-R AQ: M = 79.7; SD = 10.7]	<u>2014a; 2014b</u> 14 HC (8 F; 6 *M*) Age: 49-81 (M = 61.7; SD = 10.1); R-handed; Education NR <u>2014c</u> 12 HC (6 F; 6 *M*) Age: 40-81 (M = 63.5; SD = 9.7); R-handed; Education NR

*One participant was excluded from analysis due to contraindications for fMRI. However, demographics are based on a sample of N = 30. **Data missing for one participant.
Note: AQ - Aphasia Quotient; CT - Control Treatment; F - Female; HC - Healthy control; IT - Intention Treatment; L - Left; *M* - Male; M - Mean; NA - Not applicable; NC - Non-classifiable; NR - Not reported; R - Right; SD - Standard deviation; TC- Transcortical; Tx - Treated; UnTx - Untreated; WAB-R - Western Aphasia Battery - Revised (Kertesz, 2007)

Table 2. Characteristics of case- and case-series studies.

Study	Study Design	N*	Patient Code	Age	Sex	Education (yrs)	Handed-ness	Language(s)	Etiology	Months Post-Onset	Aphasia Type	Aphasia Severity	HC Group
Abutalebi, et al., 2009	Case study	1	JRC	56	*M*	NR; HS	R	Spanish (L1) Italian (L2)	L CVA hemorrhagic	> 1	Fluent	NR; severe anomia	NA
Crosson, et al., 2009	Case-control, MB AB crossover	5	02-030	48	F	14	R	English	L MCA CVA ischemic	8	Anomic	Mild^	5 HC (3 F; 2 M) Age: 42-74 (M = 57.60; SD = 14.88); Education: 9-18 (M = 14.20; SD = 3.63); R-handed
			03-031	74	*M*	12	R	English	L MCA CVA ischemic	83	Broca's	Moderate^	
			00-008	47	*M*	13	R	English	L MCA CVA ischemic	48	Anomic	Mild^	
			02-036	52	F	18	R	English	L CVA ICH with partial resection	15	Broca's	Severe^	
			03-004	54	F	14	R	English	L CVA hemorrhagic + ischemic	24	Broca's	Severe^	
Davis, et al., 2006	Case study	1	AT	55	*M*	14	R	English	L MCA CVA	5	Wernicke's	Severe	NA
Della Rosa, et al., 2014	Case-series	2	P1-DG	42	F	NR; HE	R	Italian	R CVA hemorrhagic	~ 1	TC Motor crossed	NR; severe anomia	NA
			P2-PZ	44	NR	NR; HE	R	Italian	L CVA hemorrhagic	~ 1	TC Motor	NR; severe anomia	
Fridriksson, et al., 2007	Case-study, MB AB crossover	3	NS	63	F	NR	NR	English	L MCA CVA ischemic	12	Conduction	Moderate^	10 HC (sex NR) Age: 35 - 77 (M = 58.3; SD NR) Education and handedness NR
			EG	42	F	NR	NR	English	L MCA CVA ischemic	22	Broca's	Severe^	
			CH	63	*M*	NR	NR	English	L CVA ischemic	98	Broca's	Moderate-severe^	
Fridriksson, et al., 2006	SSMB	3	P1	62	*M*	MA	R	English	L MCA CVA	84	Broca's	Moderate	2 (2 M) C1: 68; high school; C2: 69; college; both R-handed
			P2	68	*M*	HS	R	English	L MCA CVA	144	Broca's	Severe	
			P3	47	*M*	HS	R	English	L MCA CVA	24	Anomic	Mild-moderate	
Kiran, et al., 2015	Single-subject design with HC group	8	5	53	F (1) *M* (7)	NR	NR	English	R CVA	107	NR	Moderate^	8 HC (4 F; 4 M) Age (M = 57.5; range and SD NR) Education and handedness NR
			11	59				English	L CVA	143		Moderate^	
			15	59				English	L CVA	15		Mild^	
			32	51				English	L CVA	87		Severe^	
			33	65				English	L CVA	49		Severe^	
			62	49				English	L CVA	157		Moderate^	
			93	66				English	L CVA	24		Mild^	
			115	63				English	L CVA	98		Moderate^	
Kurland, et al., 2012	SSMB AB design	2	HBL	71	*M*	22	R	English	L MCA CVA ischemic	108	TC Motor	Moderate-severe	NA
			ITY	79	F	12	R	English	L MCA CVA ischemic	6	Broca's	Moderate-severe	
Kurland, et al., 2010	SSMB AB design	1	ACL	55	*M*	16	R	English	L MCA CVA	36	Wernicke's	Moderate	NA
Leger, et al., 2002	Case-control study	1	RC	42	*M*	NR; HE	R	French	L MCA CVA	24	Conduction	Severe	6 HC (1 F; 5 M) Age (M = 52.2; Range and SD NR); R handed; Education NR (but matched)
Leonard, et al., 2015 *[patients also in*	Case-series	2	P2	81	*M*	14	R	English	L MCA CVA	12	Broca's	Moderate-severe	NA

Truzman et al., 2021]			P4	64	*M*	12	R	English	L CVA	21	Broca's	Moderate-severe	
Marangolo, et al., 2009	Case study	1	VR	60	F	NR; HE	R	Flemish (L1) Italian (L2)	L CVA ischemic	8	NR	NR	NA
Marcotte, et al., 2018	Case-series	2	P1	59	F	NR	R	English	L MCA CVA ischemic	36	Broca's	Moderate	NA
			P2	58	*M*	NR	R	English	L MCA CVA ischemic	12	Broca's	Moderate	
Marcotte & Ansaldo, 2010	Case study	1	CM	66	*M*	18	R	French	L CVA	84	Broca's	Severe	NA
Meinzer, et al., 2008	Case-series	11	1	19	F	NR	R	German	L CVA hemorrhagic	11	Broca's	Mild	NA
			2	35	*M*				L CVA hemorrhagic	32	Broca's	Mild	
			3	49	F				L CVA ischemic	6	Broca's	Mild	
			4	55	F				L CVA ischemic	30	Not classified	Moderate	
			5	61	*M*				L CVA ischemic	48	Broca's	Moderate	
			6	60	*M*				L CVA ischemic	27	Broca's	Moderate	
			7	46	*M*				L CVA ischemic	34	Global	Severe	
			8	51	*M*				L CVA ischemic	59	Wernicke's	Moderate	
			9	56	*M*				L CVA ischemic	45	Wernicke's	Moderate	
			10	66	F				L CVA ischemic	480	Broca's	Mild	
			11	42	*M*				L CVA ischemic	19	Broca's	Moderate	
Meinzer, et al., 2007	Case study	1	CQ	35	*M*	PhD	R	French (L1) German (L2)	L MCA CVA ischemic	32	Anomic	Moderate	NA
Meinzer, et al., 2006	Case-control study	1	1	80	F	NR	NR	German	L MCA CVA ischemic	25	Wernicke's	NR; severe anomia	3 HC (3 F) Age: 76-85 (M = 80; SD = 4.5) R handed; Education NR
Peck, et al., 2004	SSMB with matched controls	3	P1	46	*M*	12	R	English	L CVA	48	Nonfluent	NR	3 HC (3 F) Age: 42, 42, 59 Education: 9, 12, 13; R-Handed
			P2	79	F	12	R	English	multiple L CVAs	44 (most recent)	Nonfluent		
			P3	48	F	14	R	English	L CVA	8	Nonfluent		
Rochon, et al., 2010 *[treated patients also in Truzman et al., 2021]*	SSMB	4 (2 Tr)	ATr1	50	F	16	R	English	L CVA	42	Broca's	NR	10 (3 F; 7 M) Age (M = 61); Education (M = 16); R handed
			ATr2	73	*M*	12	R	English	L CVA	48	Mixed nonfluent	NR	
			AUn1	83	*M*	14	R	English	L CVA	30	Wernicke's	NR	
			AUn2	63	*M*	12	R	English	L CVA	48	Anomic	NR	
Sandberg, et al., 2015	SSMB	10	P1	57	F	NR; at least HS	R	English	L MCA CVA	38	Anomic	Mild^	NA
			P2	56	*M*					76	Conduction	Mild^	
			P3	59	*M*					23	Anomic	Mild^	
			P4	47	*M*					42	Anomic	Mild^	
			P5	48	*M*					93	Conduction	Moderate^	
			P6	74	F					134	Anomic	Mild^	
			P7	53	*M*					117	Broca's	Severe^	
			P8	69	*M*					16	Anomic	Mild^	
			P9	56	F					7	Anomic	Mild^	
			P10	75	*M*					11	TC Motor	Moderate^	
Vitali, et al., 2010 [merge with Vitali et al., 2007]	Case-series	1	GR	53	*M*	13	R	Italian	L MCA CVA ischemic	48	Non-fluent agrammatic	Severe	NA

Total	**62**	**Mean**	**57.2**	**Mean**	**51.8**
		SD	*12.31*	*SD*	*67.2*

*Only eligible cases extracted (i.e., stroke etiology, neuroimaging results available). ^Severity based on WAB-AQ score and manual.
Note: AQ - Aphasia Quotient (Western Aphasia Battery - WAB; Kertesz et al., 2007); BDAE - Boston Diagnostic Aphasia Exam (Goodglass et al., 2001); CVA - Cerebrovascular Accident; F - Female; HC - Healthy control; HE - Highly educated; HS - High School; ICH - Intracerebral Hemorrhage; L1 - First language; L2 - Second Langauge; L - Left; *M* - *Male*; M - Mean; MA - Master's degree; MB - Multiple baseline; MCA - Middle Cerebral Artery; NA - Not applicable; NR - Not reported; R - Right; SSMB - Single-subject multiple baseline; TC - Transcortical; Tr - Treated; Un - Untreated.

Table 3. Summary of treatment and neuroimaging characteristics across all studies and reported naming outcomes following treatment.

Study	Authors	Study Design	N (treated)	Imaging Method	Task in scanner	Control task used for contrast	Treatment	Schedule	Significant Naming Improvement? *
1	Abel, et al., 2014 *[merge with Abel, et al., 2015]*	Parallel alternating cohort-control	14	er-fMRI WB	overt picture naming	passive viewing of fixation cross	Semantic and phonological cueing	0.3-1 hr/day x 5 days/week 4 weeks	Y
2	Abutalebi, et al., 2009	Case study	1	er-fMRI WB and ROI	overt picture naming	NR	Progressive syllabic cueing	1 hr/day x 5 days/week x 6 weeks	Y
3	Benjamin, et al., 2014	Parallel cohorts	14	er-fMRI ROI	overt category member generation	passive viewing of fixation cross	Naming + category generation IT (with complex left-hand movement) vs. CT (no left-hand movement)	10 sessions/week 3 weeks	IT: Y (in 5/6 cases) CT: Y (in 6/7 cases)
4	Bruehl, et al., 2021	Parallel alternating cohort-control	12	er-fMRI WB	overt picture naming interfered picture naming	passive viewing of fixation cross	INTA: semantic or phonological cueing with distractor priming	4 weeks	Y
5	Crosson, et al., 2009	Case-control, MB AB crossover	5	er-fMRI ROI	overt category member generation	passive viewing of fixation cross	IT (naming + complex L hand movement)[b]	1 session/day x 5 days/week 6 weeks	Y (in 4/5 cases)
6	Davis, et al., 2006	Case study	1	fMRI-block ROI	covert lexical decision, verb generation, text listening	lexical decision task	Intensive computerized semantic decision-making and categorization	1 to 1.5 hrs/day x 5 days/week 4 weeks	Y
7	Della Rosa, et al., 2014	Case-series	2	er-fMRI WB and ROI	overt picture naming	NR	Progressive syllabic cueing treatment	1 hr/day x 5 days/week 12 weeks	N
8	Durand, et al., 2021 *[merge with Durand et al., 2018]*	Cohort-control	4	er-fMRI WB (2018 paper)	overt picture (noun) and video (verb) naming	scrambled images and videos + spoken word "BABA"	POEM (verb naming, with gesture and visualization)	1 hr/day x 3 days/week 5 weeks	Y
9	Fridriksson, et al., 2012 *[merge with Fridriksson, et al., 2010]*	Parallel alternating cohorts	30	er-fMRI WB and VOI	overt picture naming	passive viewing of abstract images	Semantic and phonological cueing (alternating)	3 hr/day x 5 days/week 2 weeks	Y
10	Fridriksson, et al., 2007	Case-series; MB AB crossover	3	er-fMRI WB	overt picture naming	passive viewing of abstract images	Semantic and phonological cueing (alternating)	2 hrs/day x 5 days/week 1 week (semantic) 1 week (phonological)	Y (in 2/3 cases)
11	Fridriksson, et al., 2006	SSMB	3	er-fMRI WB	overt picture naming	passive viewing of abstract images	Group therapy: intensive hierarchical cueing (errorless approach: word repetition, phonemic cueing, naming)	4 hr/day x 5 days/week 2 weeks	N
12	Johnson, et al., 2019 *[merge with Johnson et al., 2021 and Braun et al., 2022]*	Cohort-control	26	er-fMRI ROI	overt picture naming	passive viewing of fixation cross	Semantic categorization, decision-making, feature-matching, and generative naming	2 days/week Until 90% accuracy reached, up to 12 weeks; session length NR	Y (in 17/26 cases)
13	Kiran, et al., 2015	Single-subject design with HC group	8	er-fMRI VOI	overt picture naming, semantic verification	scrambled images + spoken word "SKIP"/button press	SFA and semantic decision-making	Until 80% accuracy reached, up to 10 weeks; other details NR	Y
14	Kurland, et al., 2012	SSMB AB design	2	fMRI-block WB	overt picture naming	viewing of abstract images + spoken word "PASS"	PACE then CIAT (for object and action naming)	3 hrs/day x 5 days/week 2 weeks (PACE) + 2 weeks (CIAT)	Y

15	Kurland, et al., 2010	SSMB AB design	1	fMRI-block WB	overt picture naming	viewing of abstract images + spoken word "PASS"	CILT then PACE (for object and action naming)	3 hrs/ day x 5 days/week 2 weeks (CILT) + 2 weeks (PACE)	Y
16	Leger, et al., 2002	Case-study with HC group	1	fMRI-block WB	overt picture naming picture/written rhyme judgments	rest	Training articulatory gestures of target syllables	1 hr/day x 6 days/week 6 weeks	Y
17	Leonard, et al., 2015 *[two patients also in Truzman et al., 2021]*	Case-series	5	fMRI-block WB LV PLS analysis	covert semantic and rhyme judgments	fixation cross + button press pictured object size judgments + button press	PCA - Choice vs. No Choice conditions	1 hr/day x 3 days/week 10 weeks	Y
18	Marangolo, et al., 2009	Case study	1	er-fMRI WB	overt picture naming	NR	Picture naming with orthographic cueing	2 hrs/day x 5 days/week 2 weeks	Y
19	Marcotte, et al., 2018	Case-series	2	er-fMRI WB	overt picture naming	NR	Short-term intensive vs. standard non-intensive PCA	3 hr/day x 4 days/week 2.5 weeks	Y (in 1/2 cases)
20	Marcotte, et al., 2013 *[merge with Marcotte, et al., 2012]*	Cohort-control	9	fMRI-block WB	overt picture naming	distorted image + spoken word "BABA"	SFA	1hr/day x 3 days/week Until 80% accuracy reached, up to 6 weeks	Y
21	Marcotte & Ansaldo, 2010	Case study	1[a]	er-fMRI WB	overt picture naming	distorted image + spoken word "BABA"	SFA (nouns and verbs)	1 hr/day x 3 days/week 3 weeks	N
22	Masson-Trottier, et al., 2021	Cohort	10	rs-fMRI WB ROI-to-ROI analysis	n/a	n/a	PCA	1 hr/day x 3 days/week 5 weeks	Y
23	McKinnon, et al., 2017	Cohort	8	DKI-WB	n/a	n/a	ILAT (constraint-induced)	4 hrs/day x 5 days/week 3 weeks	Y
24	Meinzer, et al., 2008	Case-series[c]	11	fMRI-block ROI (defined by MEG)	overt picture naming	passive viewing of fixation cross	CIAT	3 hrs/day x 5 days/week 2 weeks	Y
25	Meinzer, et al., 2007	Case study	1	fMRI-block WB	overt picture naming	passive viewing of fixation cross	CIAT (in L2, German)	3 hrs/day x 5 days/week 2 weeks	N
26	Meinzer, et al., 2006	Case-control study	1	fMRI-block WB	overt picture naming	passive viewing of fixation cross	CIAT	3 hrs/day x 5 days/week 2 weeks	N
27	Menke, et al., 2009	Cohort-control	8	er-fMRI WB	overt picture naming	NR	Computer-assisted associative language learning (semantic, phonological and orthographic cues)	3 hrs/day x 5 days/week 2 weeks	Y
28	Nardo, et al., 2017	Cohort	18	er-fMRI WB	overt picture naming, cued picture naming	picture naming with noise control cue	Computerized error-reducing phonological cueing (whole word, initial phoneme)	2 hrs/day x 7 days/week 6 weeks	Y
29	Peck, et al., 2004	SSMB with matched controls	3	er-fMRI ROI time to peak (TTP) analysis	overt category member generation	NR	IT (naming + complex L hand movement) vs. AT (naming stimuli presented in left hemispace)	5 days/week 6 weeks	Y
30	Rochon, et al., 2010 *[also in Truzman et al., 2021]*	SSMB	2	fMRI-block WB LV PLS analysis	covert semantic and rhyme judgments	fixation cross + button press pictured object size judgments + button press	PCA	1 hr/day x. 3 days/week Until 80% accuracy or 15 sessions reached	Y

31	Sandberg, et al., 2015	SSMB[d]	10	er-fMRI WB and ROI/fROI	covert concreteness judgment (words)	categorical decision task (vowel vs. consonant letter strings) + button press	Semantic feature selection, concreteness judgments and synonym generation	2 hrs/day x 2 days/week Up to 10 weeks	Y (in 9/10 cases)
32	van Hees, et al., 2014a *[merge with van Hees et al., 2014b; van Hees et al., 2014c]*	Parallel alternating cohort-control[d]	8	er-fMRI WB	overt picture naming	passive viewing of scrambled line drawings	PCA and SFA	0.75-1.5 hrs/day x 3 days/week 4 weeks	Y (7/8 PCA; 4/8 SFA)
33	Vitali, et al., 2010 [merge with Vitali et al., 2007]	SSMB	1[a]	er-fMRI WB (from 2007 paper)	overt picture naming	NR	Progressive syllabic cueing	1 hr/day x 5 days/week 4 weeks	Y

*Y indicates that a significant improvement in naming was statistically shown at the group level, or for all participants at the individual level. N indicates that naming improvement were reported but not statistically demonstrated.

[a]This study treated 2 patients but one did not have stroke etiology - only data pertaining to stroke patient is reported.

[b]Although all patients received both the Intention and Control conditions in a crossover design, this study only reports findings from the IT group.

[c]Neuroimaging data were anlayzed on an individual basis, but treatment data were analyzed at the group level.

[d]Both case- and group-level neuroimaging analyses available.

Note: AT - Attention Treatment; CILT - Constraint-Induced Language Therapy; CT - Control Treatment; HC - healthy control; ILAT - Intensive Language Action Therapy; INTA - Interfered Naming Therapy for Aphasia; IT - Intention Treatment; PACE - Promoting Aphasic's Communicative Effectiveness; PCA - Phonological Components Analysis; POEM - Personalized observation, execution, and mental imagery therapy; SFA - Semantic Feature Analysis; SSMB - Single subject multiple baseline;

Table 4. Critical appraisal of all included articles (n =43) using the indicators of methodological quality developed for this review (see also Appendix A).

			MRI SEQUENCE CHARACTERISTICS				PREPROCESSING							ANALYSIS								
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
	Article	Imaging Method	Anatomical image acquired?	Sequence characteristics reported for anatomical image?	All required sequence characteristics reported for functional or diffusion imaging?	Same sequence characteristics used for all patients and/or pre and post treatment?	Spatial corrections reported?	Temporal corrections reported?	Co-registration/alignment to anatomical image (T1) reported?	Normalization or warping to MNI or Talairach template reported during pre-processing, in studies with group-level data (patient or healthy control)?	Lesion masking reported during the normalization process, in pre-processing of data?	Was spatial smoothing reported, in studies with group-level data, or single-case studies with comparisons to healthy controls?	If dMRI, more than one direction used to reconstruct fiber tracks for each voxel?	Repeated baseline scans used in analysis?	If event-related, do authors specify whether incorrect events were included or excluded?	If event-related, are numbers of correct/incorrect events reported?	Whole-brain pattern of activation reported pre and/or/to post treatment in fMRI activation studies?	In laterality index (LI) analyses, are LI measures based on whole-brain activation?	In laterality index (LI) analyses, is pattern of activation reported pre and/or/to post treatment?	Statistical tests of neuroimaging data reported pre- to post-treatment?	Correction for all reported multiple comparisons of voxels?	Treatment efficacy statistically demonstrated?
Articles accepted for data synthesis after critical appraisal																						
fMRI Activation Studies																						
1	Abel et al., 2014	er-fMRI	✓	✗	✓	✓	✗	✓	✗	✓	✗	✓	n/a	✗	✗	✗	✓	n/a	n/a	✓	✗	✓
2	Abel et al., 2015	er-fMRI	✓	✗	✓	✓	✗	✓	✗	✓	✗	✓	n/a	✗	✗	✗	✓	n/a	n/a	✓	✓	✓
3	Bruehl et al., 2021	er-fMRI	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	n/a	✗	✗	✗	✓	n/a	n/a	✓	✓	✓
4	Fridriksson, 2010	er-fMRI	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	n/a	✓	✓	✗	✓	n/a	n/a	✓	✓	✓
5	Fridriksson, et al., 2007	er-fMRI	✓	✗	✗	✓	✓	✗	✓	✗	n/a	✗[b]	n/a	✓	✓	✓	✓	n/a	n/a	✓	✓	✓
6	Kurland et al., 2012	fMRI-block	✓	✓	✗	✓	✓	✓	✓	n/a	n/a	n/a	n/a	✗	n/a	n/a	✓	✓	✓	✓	✓	✓
7	Leger et al., 2002	fMRI-block	✓	✓	✓	✓	✗	✗	✗	n/a	n/a	✓	n/a	✗	n/a	n/a	✓	n/a	n/a	✓	✗	✓
8	Marangolo et al., 2009	er-fMRI	✗	n/a	✗	✓	✗	✗	n/a	n/a	✗	n/a	n/a	✗	✗	✓	✓	n/a	n/a	✓	✓	✓
9	Marcotte et al., 2018	er-fMRI	✓	✓	✓	✓	✓	✓	✗	n/a	n/a	n/a	n/a	✗	✓	✗	✓	n/a	n/a	✓	✗	✓
10	Menke et al., 2009	er-fMRI	✓	✗	✓	✓	✓	✓	✓	✗	✓	✓	n/a	✗	✗	✗	✓	n/a	n/a	✓	✗	✓
11	Sandberg et al., 2015	er-fMRI	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	n/a	✗	✓	✓	✓	✗	✓	✓	✗	✓
12	Van Hees et al., 2014b	er-fMRI	✓	✓	✓	✓	✓	✗	✓	✓	✗	✓	n/a	✗	✓	✗	✓	n/a	n/a	✓	✓	✓
Connectivity Studies																						
13	Braun et al., 2022	dMRI, DTI	✓	✓	✓	✗	✓	n/a	✓	✗	✓	n/a	✗	✗	n/a	n/a	n/a	n/a	n/a	✓	✓	✓
14	Durand et al., 2021	rs-fMRI	✓	✓	✓	✗	✓	✓	✓	✓	✗	✗	n/a	✗	n/a	n/a	n/a	n/a	n/a	✓	✓	✓
15	Masson-Trottier et al., 2021	rs-fMRI	✓	✓	✓	✗	✓	✓	✓	✓	✗	✗	n/a	✗	n/a	n/a	n/a	n/a	n/a	✓	✓	✓
16	McKinnon et al., 2017	DKI	✓	✓	✓	✓	✗	n/a	✓	✓	✓	n/a	✗	n/a	n/a	n/a	n/a	n/a	n/a	✓	✓	✓

17	Van Hees et al., 2014a	dMRI, HARDI	✓	✗	✓	✓	✓	n/a	✗	n/a	✗	n/a	✓	✗	n/a	n/a	n/a	n/a	n/a	✓	✗	✓
18	Van Hees et al., 2014c	rs-fMRI	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	n/a	✗	n/a	n/a	n/a	n/a	n/a	✓	✓	✓
All articles accepted for initial review																						
19	Abutalebi et al., 2009	er-fMRI	✓	✓	✓	✓	✓	✓	✓	n/a	n/a	n/a	n/a	✗	✓	?	✓	n/a	n/a	✗	✗	✓
20	Benjamin et al., 2014	er-fMRI	✓	✓	✓	✓	✗	✗	✗	✓	✓	✗	n/a	✗	✗	✗	n/a	✗	✓	✓	✗	✓
21	Crosson et al., 2009	er-fMRI	✓	✓	✓	✓	✓	✗	✓	n/a	✗	✗	n/a	✗	✓	✓	✗	✗	✓	✓	✗	✓
22	Davis et al., 2006	fMRI-block	✓	✓	✓	✓	✓	✗	✗	n/a	✗	n/a	n/a	✗	n/a	n/a	✗	✗	✓	✓	✗	✓
23	Della Rosa et al., 2014	er-fMRI	✓	✓	✓	✓	✓	✓	✓	n/a	n/a	n/a	n/a	✗	✓	✓	✓	n/a	n/a	✓	✗	✗
24	Durand et al., 2018	er-fMRI	✓	✓	✓	✗	✓	✓	✗	n/a	✓	n/a	n/a	✗	✓	✓[a]	✓	✓	✓	✗	✗	✓
25	Fridriksson et al., 2012	er-fMRI	✓	✓	✓	✓	✓	✗	✗	✓	✓	✓	n/a	✓	✓	✓	✗	n/a	n/a	✓	✓	✓
26	Fridriksson, et al., 2006	er-fMRI	✓	✓	✓	✓	✓	✗	✓	n/a	n/a	✓	n/a	✓	✓	✓	✓	n/a	n/a	✓	✓	✗
27	Johnson et al., 2019	er-fMRI	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	n/a	✗	✗	✗	✗	n/a	n/a	✓	✗	✓
28	Johnson et al., 2021	er-fMRI	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	n/a	✗	✗	✓	✗	n/a	n/a	✓	✗	✓
29	Kiran et al., 2015	er-fMRI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	n/a	✗	✗	✗	✗	n/a	n/a	✓	✗	✓
30	Kurland et al., 2010	fMRI-block	✓	✓	✓	✓	✓	✓	✓	n/a	✓	n/a	n/a	✗	n/a	n/a	✓	n/a	n/a	✗	✓	✓
31	Leonard et al., 2015	fMRI-block	✓	✗	✓	✓	✓	✗	✓	n/a	n/a	n/a	n/a	✗	n/a	n/a	✓	n/a	n/a	✗	✗	✓
32	Marcotte et al., 2013	fMRI-block	✓	✓	✗	✓	✓	✓	✗	✓	✗	✓	n/a	✗	n/a	n/a	n/a	n/a	n/a	✓	✗	✓
33	Marcotte et al., 2012	er-fMRI	✓	✓	✓	✓	✓	✓	✗	✓	✗	✓	n/a	✗	✓	✓[a]	✓	n/a	n/a	✗	✗	✓
34	Marcotte & Ansaldo, 2010	er-fMRI	✓	✗	✗	✓	✗	✗	✗	n/a	✗	n/a	n/a	✗	✓	✓[a]	✓	n/a	n/a	✗	✗	✗
35	Meinzer et al., 2008	fMRI-block	✓	✗	✗	✓	✓	✓	✗	n/a	n/a	n/a	n/a	✗	n/a	n/a	✗	n/a	n/a	✓	✗[c]	✓
36	Meinzer et al., 2007	fMRI-block	✗	n/a	✗	✓	✓	✓	n/a	n/a	n/a	n/a	n/a	✗	n/a	n/a	✓	n/a	n/a	✓	✗	✗
37	Meinzer et al., 2006	fMRI-block	✓	✗	✗	✓	✓	✓	✗	n/a	n/a	✓	n/a	✗	n/a	n/a	✓	n/a	n/a	✓	✗	✗
38	Nardo et al., 2017	er-fMRI	✗	n/a	✗	✓	✓	✗	n/a	✓	✓	✓	n/a	✗	✓	✓	✓	n/a	n/a	✗	✓	✓
39	Peck et al., 2004	er-fMRI	✓	✓	✓	✓	✓	✓	✗	n/a	✗	n/a	n/a	✗	✓	✓	✗	n/a	n/a	✓	✗	✓
40	Rochon et al., 2010	fMRI-block	✓	✗	✓	✓	✓	✗	✗	✓	n/a	✗	n/a	✗	n/a	n/a	✓	n/a	n/a	✗	✗	✓
41	Truzman et al., 2021	fMRI-block	✓	✗	✓	✓	✓	✗	✓	✓	✗	✓	n/a	✗	n/a	n/a	n/a	n/a	n/a	✓	✗	✓
42	Vitali et al., 2010	er-fMRI	✓	✗	✓	✓	✓	✗	✗	n/a	n/a	n/a	n/a	✗	✓	✓	n/a	n/a	n/a	✓	✗	✓
43	Vitali et al., 2007	er-fMRI	✓	✗	✓	✓	✓	✗	✗	n/a	✓	n/a	n/a	✗	✓	✗	✓	n/a	n/a	✗	✗	✓

Note. ✓ - Yes; ✗ - No; ? - Unclear; DKI - Diffusion Kurtosis Imaging; dMRI - diffusion Magnetic Resonance Imaging; er - event-related; fMRI - functional Magnetic Resonance Imaging; HARDI - High Angular Resolution Diffusion Imaging.

[a]Although the number of correct and incorrect events is reported, the authors do not report the number of correct/incorrect events for the control in-scanner condition, which required a verbal response.

[b]Spatial smoothing was completed for HC group, but not for patient group.

[c]Corrections for multiple comparisons were applied to all but three participants.

Table 5. Counts of reported regions with significant increases in activation after therapy (post- versus pre-treatment contrasts). Activations with and without multiple correction comparisons are shown for case- and group-level data.

					CASE				GROUP		GROUP Correlated with Treatment			
		Atlas ID			All		MC Corr.		All		All		MC Corr.	
Lobe	Gyrus	Left	Right	Anatomical/Cyto-architectonic descriptions	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Frontal Lobe	SFG, Superior Frontal Gyrus	1	2	*medial area 8*		1		1						
		3	4	*dorsolateral area 8*	3	1	3	1			1		1	
		5	6	*lateral area 9*		2		2		1				
		9	10	*medial area 6*		1		1	1					
		11	12	*medial area 9*					1					
		13	14	*medial area 10*	3		3							
	MFG, Middle Frontal Gyrus	15	16	*dorsal area 9/46*	2		2							
		17	18	*inferior frontal junction*							2		2	
		23	24	*ventrolateral area 8*					1					
		27	28	*lateral area10*	1		1							
	IFG, Inferior Frontal Gyrus	29	30	*dorsal area 44*					1					
		33	34	*caudal area 45*	2		2							
		39	40	*ventral area 44*		1		1						
	OrG, Orbital Gyrus	41	42	*medial area 14*	2		2							
		49	50	*area 13*	1	1		1						
		51	52	*lateral area 12/47*	1	1	1	1						
	PrG, Precentral Gyrus	57	58	*area 4(upper limb region)*	2		2							
		61	62	*area 4(tongue and larynx region)*		1		1						
		63	64	*caudal ventrolateral area 6*	1									
	PCL, Paracentral Lobule	65	66	*area1/2/3 (lower limb region)*	1		1		1					
				Frontal Lobe Total	***19***	***9***	***17***	***9***	***5***	***1***	***3***	***0***	***3***	***0***
Temporal Lobe	STG, Superior Temporal Gyrus	73	74	*TE1.0 and TE1.2*					3					
		79	80	*rostral area 22*	1		1							
	MTG, Middle Temporal Gyrus	83	84	*rostral area 21*	1		1							
		87	88	*anterior superior temporal sulcus*	1		1			1				
	ITG, Inferior Temporal Gyrus	89	90	*intermediate ventral area 20*	1		1							
	FuG, Fusiform Gyrus	103	104	*rostroventral area 20*	1	1	1	1						
		105	106	*medioventral area37*	2	2	2	2			1	1		
		107	108	*lateroventral area37*	2		2		1					
	PhG, Parahippocampal Gyrus	109	110	*rostral area 35/36*		1		1						
				Temporal Lobe Total	***9***	***4***	***9***	***4***	***4***	***1***	***1***	***1***	***0***	***0***
Parietal Lobe	SPL, Superior Parietal Lobule	127	128	*caudal area 7*	2	4	2	4						
		129	130	*lateral area 5*	1		1							
		131	132	*postcentral area 7*		4		4						
		133	134	*intraparietal area 7(hIP3)*	1		1					1		

	IPL, Inferior Parietal Lobule	135	136	*caudal area 39(PGp)*		2		2							
		137	138	*rostrodorsal area 39(Hip3)*	2	2	1	2	1		1		1		
		139	140	*rostrodorsal area 40(PFt)*	2	1	2	1		1	1		1		
		141	142	*caudal area 40(PFm)*	1		1								
		143	144	*rostroventral area 39(PGa)*	3		3		1	1	1		1		
		145	146	*rostroventral area 40(PFop)*		1		1	1						
	Pcun, Precuneus	147	148	*medial area 7(PEp)*	2		2				1		1		
		149	150	*medial area 5(PEm)*	2	2	2	2							
		151	152	*dorsomedial parietooccipital sulcus(PEr)*	2	1	2	1	2						
		153	154	*area 31 (Lc1)*	2	3	2	3	1						
	PoG, Postcentral Gyrus	155	156	*area 1/2/3(upper limb, head and face region)*		1		1		1					
		157	158	*area 1/2/3(tongue and larynx region)*	1	1	1	1		1					
		159	160	*area 2*	1	1	1	1							
		161	162	*area1/2/3(trunk region)*	1		1								
				Parietal Lobe Total	***23***	***23***	***22***	***23***	***6***	***4***	***4***	***1***	***4***	***0***
Insular Lobe	INS, Insular Gyrus	163	164	*hypergranular insula*	1		1			1					
		169	170	*ventral dysgranular and granular insula*	1		1								
				Insula Total	***2***	***0***	***2***	***0***	***0***	***1***	***0***	***0***	***0***	***0***
Limbic Lobe	CG, Cingulate Gyrus	175	176	*dorsal area 23*	2		2		1	1					
		177	178	*rostroventral area 24*	1	2	1	2							
		181	182	*ventral area 23*		1		1							
		185	186	*caudal area 23*	1		1								
				CG Total	***4***	***3***	***4***	***3***	***1***	***1***	***0***	***0***	***0***	***0***
Occipital Lobe	MVOcC, MedioVentral Occipital Cortex	193	194	*caudal cuneus gyrus*		1		1							
		197	198	*ventromedial parietooccipital sulcus*	1	2	1	2							
	LOcC, lateral Occipital Cortex	203	204	*occipital polar cortex*	2		2								
		205	206	*inferior occipital gyrus*	2		2								
		207	208	*medial superior occipital gyrus*	1	2	1	2							
		209	210	*lateral superior occipital gyrus*						1					
				Occipital Lobe Total	***6***	***5***	***6***	***5***	***0***	***1***	***0***	***0***	***0***	***0***
Subcortical Nuclei	Amyg, Amygdala	211	212	*medial amygdala*		1		1							
	Hipp, Hippocampus	215	216	*rostral hippocampus*							1				
		217	218	*caudal hippocampus*	2	2	2	2	1			1			
	BG, Basal Ganglia	223	224	*nucleus accumbens*		1									
		225	226	*ventromedial putamen*		1		1							
		227	228	*dorsal caudate*	4	1	4	1	1	2					
		229	230	*dorsolateral putamen*	2		2								
	Tha, Thalamus	231	232	*medial pre-frontal thalamus*	1		1		1						
		237	238	*rostral temporal thalamus*	1		1								
		241	242	*occipital thalamus*					1	1					
				Subcortical Nuclei Total	***10***	***6***	***10***	***5***	***4***	***3***	***1***	***1***	***0***	***0***
Cerebellum	Lobule I-IV	**247**	**248**	I-IV	1	1	1	1							
	Lobule V	**249**	250	V							1				

Lobule VI	**251**	253	VI	2		2									
Crus II	**257**	259	Crus II	2	2	2	2								
Lobule VIIIa	263	**265**	VIIIa		2		2								
Lobule IX	**269**	**271**	IX	1	1	1	1								
			Cerebellum Total	***6***	***6***	***6***	***6***	***0***	***0***	***1***	***0***	***0***	***0***
			Hemisphere Totals	**79**	**56**	**76**	**55**	**20**	**12**	**10**	**3**	**7**	**0**

MNI coordinates extracted from all eligible studies were labelled using the Human Brainnetome Atlas (Fan et al., 2016). There were no eligible group studies reporting post versus pre contrasts that corrected for all multiple comparisons.

Table 6. Counts of reported regions with significant decreases in activation after therapy (pre- versus post-treatment contrasts). Activations with and without multiple correction comparisons are shown for case- and group-level data.

					CASE				GROUP				GROUP Correlated with Treatment			
		Atlas ID			All		MC Corr.		All		MC Corr.		All		MC Corr.	
Lobe	Gyrus	Left	Right	Anatomical/Cyto-architectonic descriptions	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Frontal Lobe	Superior Frontal Gyrus (SFG)	1	2	*medial area 8*	2		2									
	Middle Frontal Gyrus (MFG)	17	18	*inferior frontal junction*					3		3					
		21	22	*ventral area 9/46*		2		2								
		23	24	*ventrolateral area 8*		1		1								
	Inferior Frontal Gyrus (IFG)	35	36	*rostral area 45*	1		1									
		37	38	*opercular area 44*												
		39	40	*ventral area 44*		2		2								
	Orbital Gyrus (OrG)	51	52	*lateral area 12/47*	1		1									
	Precentral Gyrus (PrG)	53	54	*area 4(head and face region)*	2		1		1		1					
		55	56	*caudal dorsolateral area 6*					1		1					
		57	58	*area 4(upper limb region)*	1								1			
		63	64	*caudal ventrolateral area 6*		1		1								
	Paracentral Lobule (PCL)	65	66	*area1/2/3 (lower limb region)*												
		67	68	*area 4, (lower limb region)*	1				2		2		1			
				Frontal Lobe Total	***8***	***6***	***5***	***6***	***7***	***0***	***7***	***0***	***2***	***0***	***0***	***0***
Temporal Lobe	Superior Temporal Gyrus (STG)	69	70	*medial area 38*	1		1									
		71	72	*area 41/42*	2		2									
		73	74	*TE1.0 and TE1.2*		1		1								
		75	76	*caudal area 22*									1			
		77	78	*lateral area 38*	1		1									
		79	80	*rostral area 22*		2		2								
	Middle Temporal Gyrus (MTG)	85	86	*dorsolateral area 37*	2	1	2	1								
		87	88	*anterior superior temporal sulcus*		1		1		1		1				
	Fusiform Gyrus (FuG)	105	106	*medioventral area37*		1		1	1	2	1	2				
	Parahippocampal Gyrus (PhG)	113	114	*lateral posterior parahippocampal gyrus*	2		2									
				Temporal Lobe Total	***8***	***6***	***8***	***6***	***1***	***3***	***1***	***3***	***1***	***0***	***0***	***0***
Parietal Lobe	Superior Parietal Lobule (SPL)	127	128	*caudal area 7*					1		1					
		129	130	*lateral area 5*					2		2					
	Inferior Parietal Lobule (IPL)	135	136	*caudal area 39(PGp)*						1		1				
		137	138	*rostrodorsal area 39(Hip3)*												
		139	140	*rostrodorsal area 40(PFt)*					1		1		2			
		141	142	*caudal area 40(PFm)*	2		2									
		145	146	*rostroventral area 40(PFop)*	2		2						3			
	Precuneus (Pcun)	147	148	*medial area 7(PEp)*						1		1	1		1	
		149	150	*medial area 5(PEm)*		1				1		1				

		151	152	*dorsomedial parietooccipital sulcus(PEr)*						1		1	1	1	1	1
		153	154	*area 31 (Lc1)*		1		1		1		1				
	Postcentral Gyrus (PoG)	155	156	*area 1/2/3(upper limb, head and face region)*	1		1									
		159	160	*area 2*					1		1					
				Parietal Lobe Total	***5***	***2***	***5***	***1***	***5***	***5***	***5***	***5***	***7***	***1***	***2***	***1***
Limbic Lobe	Cingulate Gyrus (CG)	175	176	*dorsal area 23*	1		1		1		1					
		179	180	*pregenual area 32*		2		2								
		181	182	*ventral area 23*						1		1				
		183	184	*caudodorsal area 24*	2		2		1	1	1	1				
				CG Total	***3***	***2***	***3***	***2***	***2***	***2***	***2***	***2***	***0***	***0***	***0***	***0***
Occipital Lobe	MedioVentral Occipital Cortex (MVOcC)	193	194	*caudal cuneus gyrus*	2		2									
		195	196	*rostral lingual gyrus*		1			1	1	1	1		2		2
		197	198	*ventromedial parietooccipital sulcus*		1								1		1
	Lateral Occipital Cortex (LOcC)	199	200	*middle occipital gyrus*									1			
		201	202	*area V5/MT+*									1			
		207	208	*medial superior occipital gyrus*									1		1	
		209	210	*lateral superior occipital gyrus*						2		2				
				Occipital Lobe Total	***2***	***2***	***2***	***0***	***1***	***3***	***1***	***3***	***3***	***3***	***1***	***3***
Subcortical Nuclei	Hippocampus (Hipp)	217	218	*caudal hippocampus*						1		1				
	Basal Ganglia (BG)	227	228	*dorsal caudate*		1		1								
	Thalamus (Tha)	241	242	*occipital thalamus*						1		1				
				Sucortical Nuceli Total	***0***	***1***	***0***	***1***	***0***	***2***	***0***	***2***	***0***	***0***	***0***	***0***
Cerebellum	Lobule V	249	250	*V*					1	1	1	1				
	Lobule VI	251	253	*VI*					2		2			1		1
	Crus II	257	259	*Crus II*		1		1								
				Cerebellum Total	***0***	***1***	***0***	***1***	***3***	***1***	***3***	***1***	***0***	***1***	***0***	***1***
				Hemisphere Totals	**26**	**20**	**23**	**17**	**19**	**16**	**19**	**16**	**13**	**5**	**3**	**5**

MNI coordinates extracted from all eligible studies were labelled using the Human Brainnetome Atlas (Fan et al., 2016).
MC Corr. columns represent activations only from studies that corrected for multiple comparisons.

Figure 1. PRISMA flow diagram of literature retrieval process (adapted from Moher, et al., 2009).

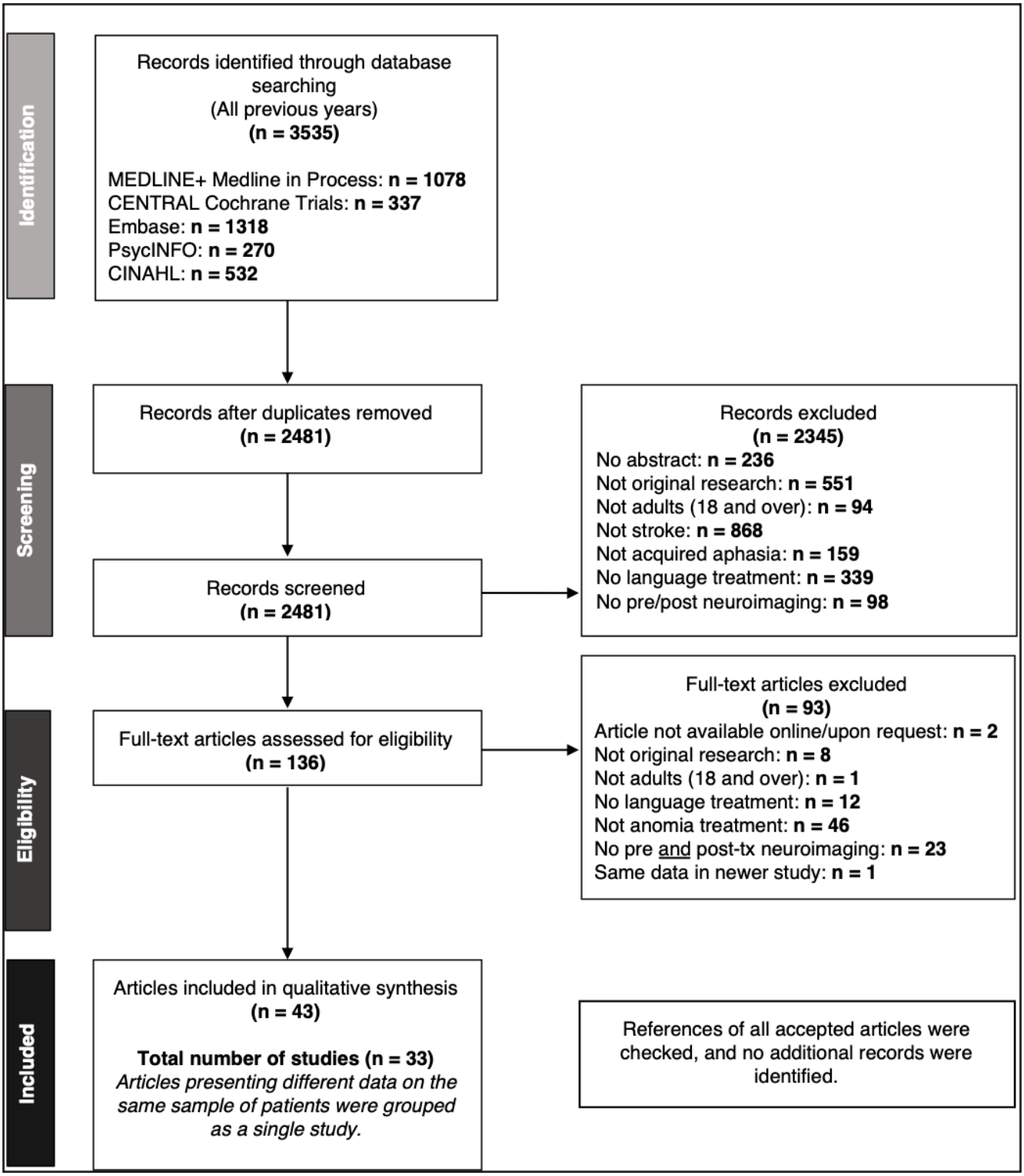


Figure 2. Summary of methodological quality indicators across all articles accepted for review. Detailed scoring procedures for each item are presented in Appendix A and scores for each individual article are presented in Table 4.

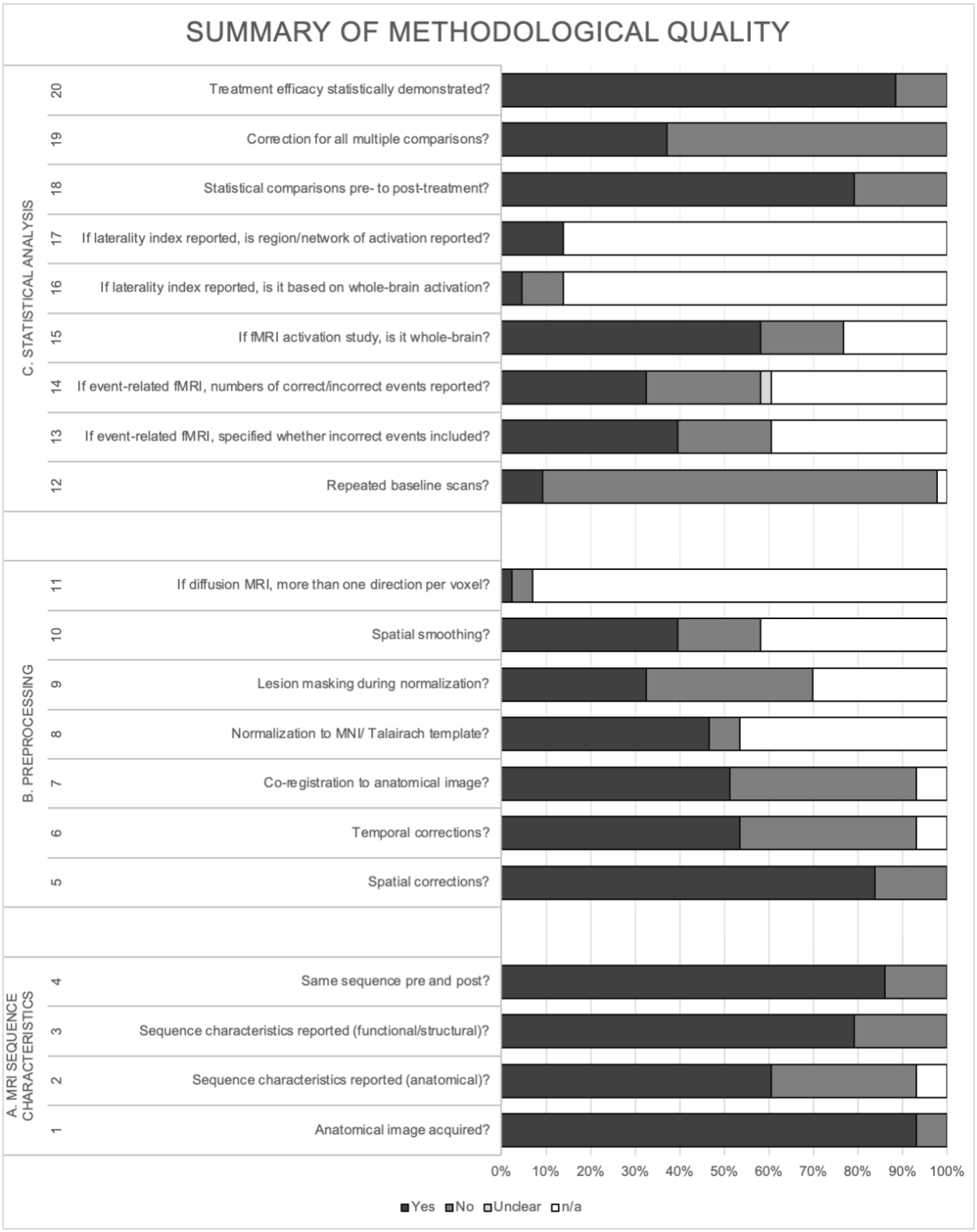
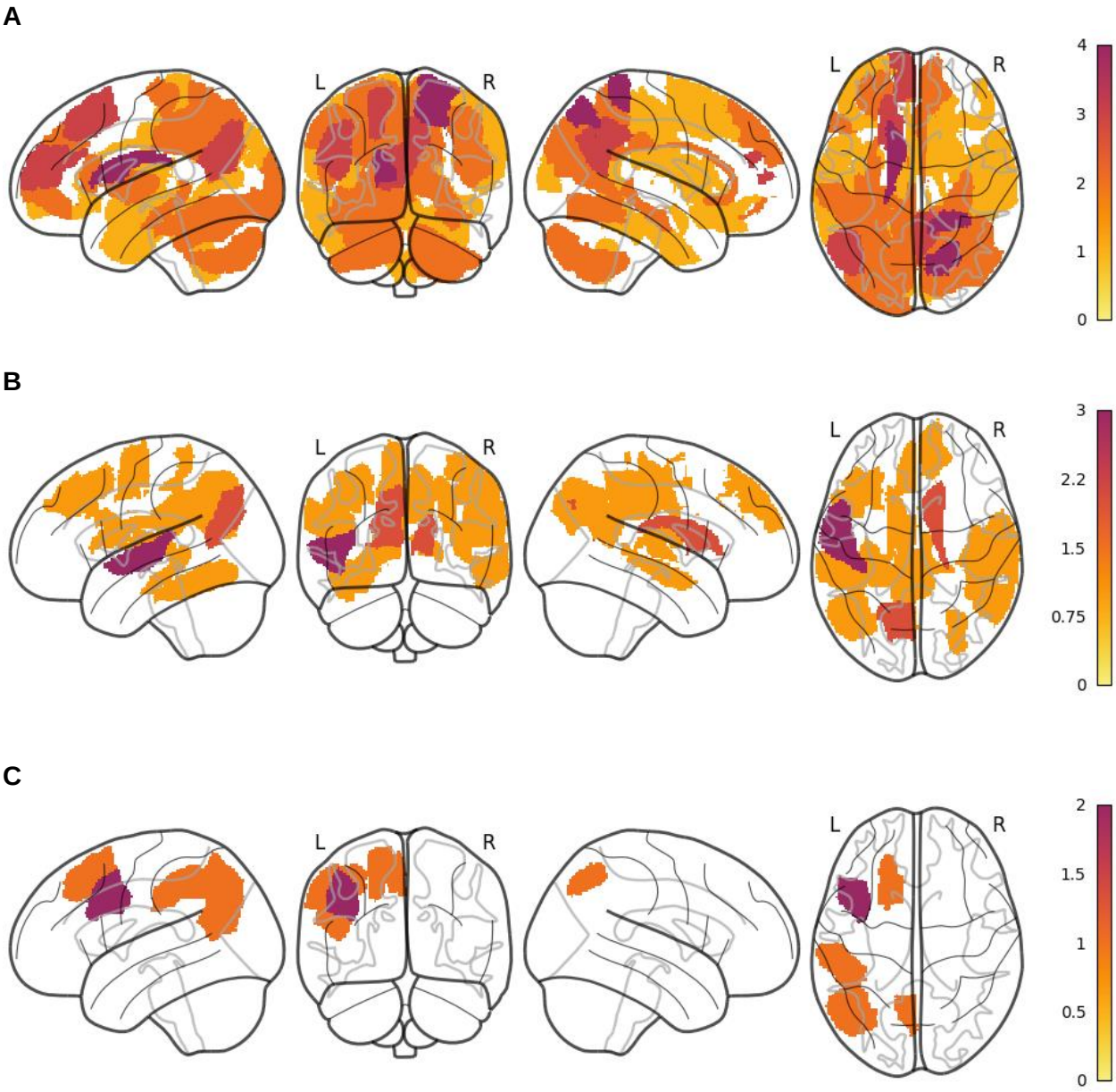
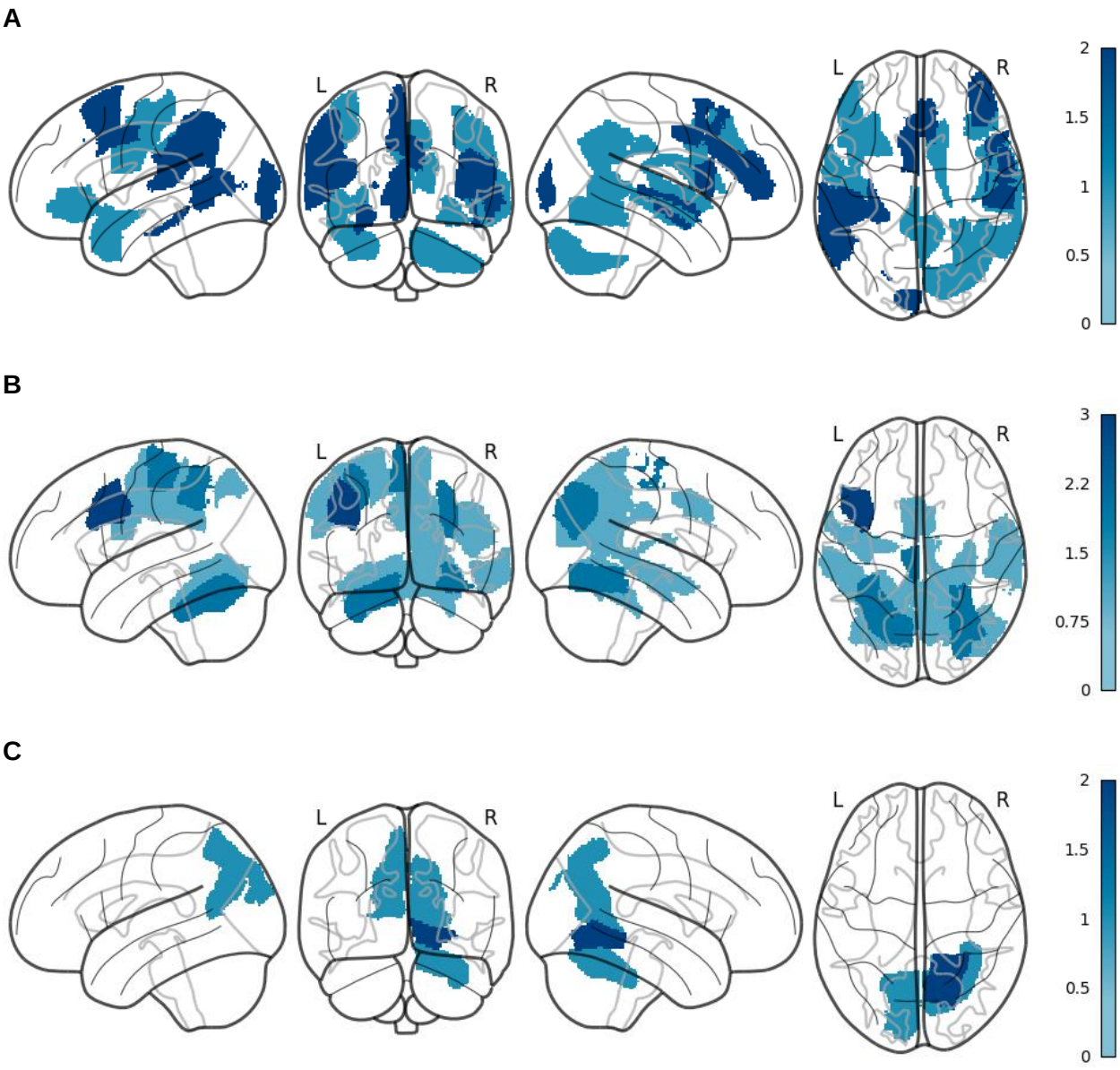


Figure 3. Summary of task-based fMRI findings showing significant increases in activation after therapy (i.e., post- versus pre-treatment contrasts), for (A) case studies, (B) group studies, and (C) group studies correlating increases in activation with improvements in naming.



Note: Count data are represented in the Figure. Darker colors indicate regions that were more frequently reported to show increased activation after therapy. Panels (A) and (C) include only activations corrected for multiple comparisons. Panel (B) includes all activations from the studies selected for data synthesis, because no activations were available after removing those not corrected for multiple comparisons. These data correspond to the data presented in Table 5. Images were created using The Human Brainnetome Atlas (Fan et al., 2016) and Glass Brain plotting from Nilearn version 0.10.1.

Figure 4. Summary of task-based fMRI findings showing significant decreases in activation after therapy (i.e., pre- versus post-treatment contrasts), for (A) case studies, (B) group studies, and (C) group studies correlating increases in activation with improvements in naming.



Note: Count data are represented in the Figure. Darker colors indicate regions that were more frequently reported to show decreased activation after therapy. Panels include only activations corrected for multiple comparisons. These data correspond to the data presented in Table 6. Images were created using The Human Brainnetome Atlas (Fan et al., 2016) and Glass Brain plotting from Nilearn version 0.10.1.

Appendix A. Detailed description of indicators developed to assess methodological quality of reporting across studies.

		METHODOLOGICAL QUALITY INDICATOR	SCORING INSTRUCTIONS
MRI SEQUENCE CHARACTERISTICS	1	Anatomical image acquired (y/n)?	Score (✓) if authors have reported acquisition of an anatomical image. Score (X) if not reported.
	2	Sequence characteristics reported for anatomical image (y/n)?	Score (✓) if authors have reported all of: 1) MRI scanner make/model, field strength; 2) TR; 3)TE; 4) voxel size OR matrix size; 5) slice thickness OR number of slices and field of view. In all other cases, score (✗).
	3	All required sequence characteristics reported for functional or diffusion imaging (y/n)?	Score (✓) if authors have reported all of: 1) MRI scanner make/model, field strength; 2)TR; 3)TE (not to be replaced by TA); 4) voxel size OR matrix size; 5) slice thickness OR number of slices OR field of view; 6) number of volumes (or ability to derive from TR, fMRI task time, ISI, or seconds per trial reported); if dMRI study, b0 or number of b0 directions. In all other cases, score (✗).
	4	Same sequence characteristics used for all patients and/or pre and post treatment?	Score (✓) if group studies or group analyses of data use same sequence characteristics within (pre/post) and across patients, as applicable. For case studies or individual analyses of data, same sequence characteristics must be used within (pre/post) but not necessarily across patients. The same principles apply in studies where patient data is analyzed individually, and healthy control data is analyzed as a group. Give a score of (✗) only if study explicitly states that a different scanner was used for a subset of the sample, or pre and post treatment. If scanner was updated during the study, but no details are given regarding when update occurred or for which patients, score (✗).
PREPROCESSING	5	Spatial corrections reported (y/n)?	In task-based functional MRI studies, score (✓) if study reports spatial correction (e.g., maximum acceptable movement (mm), realignment or correction of head motion in overt tasks). In dMRI studies, score (✓) if study reports spatial corrections (i.e., movement - blurring, ringing, striping) and/or distortions and eddy current. This indicator is not relevant with a single anatomical MRI image. This indicator applies equally to whole brain and ROI studies
	6	Temporal corrections reported (y/n)?	For functional MRI studies, score (✓) if study reports temporal correction (i.e., slice timing). For all other study types (diffusion/structural imaging), give a score of n/a.
	7	Co-registration/alignment to anatomical image (T1) reported?	Score (✓) if study makes any mention of co-registration or alignment of functional images to an anatomical (T1) image. Score (✗) if study reports acquisition of anatomical and functional images but does not explicitly report co-registration.
	8	Normalization or warping to MNI or Talairach template reported during pre-processing, in studies with group-level data (patient or healthy control)?	Score (✓) if normalization is mentioned in pre-processing step; specific template does not have to be named, as long as the term "template" is used. If MNI coordinates are presented in results, you can assume that it was normalized to MNI space. Studies may refer to this step as "co-registration to ___ template". Score (✗) if normalization was not reported in pre-processing. Score (n/a) In a single-case study with individual fMRI data analyses. In studies where patient sample is an individual-level analysis, but healthy control sample is a group-level analysis, then rate whether normalization is reported for the group-level analysis (i.e., wherever applicable).
	9	Lesion masking reported during the normalization process, in pre-processing of data?	Score (✓) if studies report masking, lesion masking, lesion correction, or mention accounting for the lesion during the normalization/warping process, during pre-processing (i.e., not lesion-masking of results). Score this item if a case-series study reports group analyses of the neuroimaging data. Score (n/a) if no normalization was done (which is only acceptable for individual-level data analyses). Some single case studies nevertheless report normalization procedures and lesion masking; in these cases, score as (n/a).
	10	Was spatial smoothing reported, in studies with group-level data, or single-case studies with comparisons to healthy controls?	Score (✓) if studies report spatial smoothing for group analyses of (patient or healthy control) neuroimaging data. Score (n/a) in single-case studies with individual fMRI analyses and no comparisons to healthy controls.
	11	If dMRI, more than one direction used to reconstruct fiber tracks for each voxel?	If study uses DTI, score (X). If study uses other diffusion approaches (e.g., HARDI), score (✓).

STATISTICAL ANALYSIS	**12**	Repeated baseline scans used in analysis?	Score (✓) if study reports multiple baseline scans and uses these in statistical analysis of neuroimaging data. Otherwise, score (✗).
	13	If event-related, do authors specify whether incorrect events were included or excluded?	Score (✓) if any portion of the study (text or tables) indicate that only correct items were used in fMRI analysis. Score (n/a) for fMRI block designs.
	14	If event-related, are numbers of correct/incorrect events reported?	Score (✓) if total number of items is indicated or can be derived from reported percentages/data. Score (X) if the total number of items is not indicated and cannot be inferred. Graphic demonstrations (in a figure) are not adequate unless accompanied by specific numbers in a table or in the text.
	15	Whole-brain pattern of activation reported pre to post treatment in fMRI activation studies?	Score (✓) if whole brain analysis is reported, if both whole-brain and ROI analyses are reported, or if study masked deactivated regions in post-processing, but reports data on whole-brain imaging. In general, be conservative in scoring and only score (✓) when whole-brain results are presented. Score (✗) if ROI or VOI analyses reported only. Score (n/a) if the study's only neuroimaging outcome is a laterality index (LI) or a connectivity measure (e.g., DCM, FC).
	16	In laterality index (LI) analyses, are LI measures based on whole-brain activation?	In studies using LI as an outcome, score (✓) if LI calculations are based on whole-brain data, and score (✗) if LI calculations are based on ROIs. Score n/a for studies that do not report LI measures.
	17	In laterality index (LI) analyses, is pattern of activation reported pre and/or/to post treatment?	For studies reporting a laterality index, score (✓) if the study indicates the locations/regions/network of primary activation pre- and post-treatment. Score (✗) if only LI analysis is presented, but it isn't clear to reader whether this hemispheric difference is associated with the language network. Score (n/a) for studies that do not report LI.
	18	Statistical tests of neuroimaging data reported pre- to post-treatment?	Pre- and post-treatment statistical comparisons ensure that each subject acts as their own control, with respect to neuroimaging variables. Score (✓) if study directly compares pre- to- post-treatment neuroimaging findings, otherwise score (✗)
	19	Correction for <u>all reported</u> multiple comparisons of voxels?	Score as (✓) if study mentions correction for multiple comparisons. Acceptable corrections include: family-wise error rate (FWER), Bonferroni, false discovery rate (FDR); corrections made at cluster level are acceptable. Score as (✗) if: not specified in paper, not all tests were corrected, high threshold applied but no corrections made, no threshold levels are reported, if only one of the study groups was corrected (but not the other), or if uncorrected thresholds are inserted post-hoc, when activations do not reach corrected thresholds.
	20	Treatment efficacy statistically demonstrated?	Score as (✓) if study demonstrates statistically significant improvements in naming. Score (✗) if study reports improvements in naming but they are not statistically demonstrated, or if study reports no significant improvement in naming after therapy.

Development of methodological quality indicators was based on published guidelines and recommendations for reporting in fMRI studies (Poldrack et al., 2008), and neuroimaging in aphasia research (Meinzer et al., 2013).

SUPPLEMENTARY MATERIALS

Supplementary Table 1. MEDLINE Search Strategy

	Search Term
1	aphasia/ or exp aphasia, broca/ or exp aphasia, conduction/ or exp aphasia, wernicke/
2	exp Anomia/
3	aphasi$.mp,kw.
4	dysphasi$.mp,kw.
5	(anomic or anomia).mp,kw.
6	exp Language Disorders/
7	speech disorders/
8	((speech or language or linguistic) adj5 (disorder$ or impair$ or problem$ or dysfunction)).mp,kw.
9	language therapy/
10	speech therapy/
11	((speech or language or aphasi$ or dysphasi$) adj5 (therap$ or train$ or rehabilitat$ or treat$ or remediat$ or pathol$)).mp,kw.
12	remedial therap$.mp,kw.
13	Th.fs.
14	magnetic resonance imaging.mp. or exp Magnetic Resonance Imaging/
15	(MRI or MRi or NMRI or NMRi).mp.
16	((magn* or MR or NMR or spin or diffus*) adj3 (imag* or scan* or resonance*)).mp.
17	exp Diffusion Magnetic Resonance Imaging/ or exp White Matter/ or diffusion imaging.mp. or exp Diffusion Tensor Imaging/
18	((structural adj2 MR*) or volum* ajd2 MR* or (functional adj2 MR*) or (diffusion adj2 MR*) or "sMRI" or "vMRI" or "fMRI" or "dMRI").mp.
19	exp Neuroimaging/ or neuroimag*.mp.
20	(exp child/ or exp infant/) not ((exp child/ or exp infant/) and (exp adolescent/ or exp aged/ or exp adult/))
21	(animals not (humans and animals)).sh.
22	or/1-8
23	or/9-13
24	or/14-19
25	22 and 23 and 24
26	25 not 20
27	26 not 21

Supplementary Material. Complete list of excluded full-text articles (n = 93).

1. Abo, M., Senoo, A., Watanabe, S., Miyano, S., Doseki, K., Sasaki, N., Kobayashi, K., Kikuchi, Y., & Yonemoto, K. (2004). Language-related brain function during word repetition in post-stroke aphasics. *Neuroreport*, *15*(12), 1891–1894.
2. Baliki, M. N., Babbitt, E. M., Cherney, L. R., & Harvey, R. L. (2018). Brain network topology influences response to intensive comprehensive aphasia treatment. *NeuroRehabilitation*, *43*(1), 63–76. rzh. https://doi.org/10.3233/NRE-182428
3. Babbitt, E. M., Cherney, L. R., Wang, X., & Pitts, L. L. (2021). Extended fmri-guided anodal and cathodal transcranial direct current stimulation targeting perilesional areas in post-stroke aphasia: A pilot randomized clinical trial. *Brain Sciences*, *11*(3), 1–24. https://doi.org/10.3390/brainsci11030306
4. Barbieri, E., Mack, J., Chiappetta, B., Europa, E., & Thompson, C. K. (2019). Recovery of offline and online sentence processing in aphasia: Language and domain-general network neuroplasticity. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *120*(dsp, 0100725), 394–418. https://doi.org/10.1016/j.cortex.2019.06.015
5. Bonilha, L., Gleichgerrcht, E., Nesland, T., Rorden, C., & Fridriksson, J. (2016). Success of Anomia Treatment in Aphasia Is Associated With Preserved Architecture of Global and Left Temporal Lobe Structural Networks. *Neurorehabilitation and Neural Repair*, *30*(3), 266–279. https://doi.org/10.1177/1545968315593808
6. Bonilha, L., Hillis, A. E., Wilmskoetter, J., Hickok, G., Basilakos, A., Munsell, B., Rorden, C., & Fridriksson, J. (2019). Neural structures supporting spontaneous and assisted (entrained) speech fluency. *Brain: A Journal of Neurology*, *142*(12), 3951–3962. rzh. https://doi.org/10.1093/brain/awz309
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Supplementary Table 2. Narrative summary of all studies accepted in stage one of the review but excluded from data synthesis at stage two.

Study	Study Design	N (scanned)	Treatment	Imaging Method	Task in scanner	Methodological Quality Score (from Table 4)	Summary of main findings
Abutalebi, et al., 2009	Case study	1	Progressive syllabic cueing	er-fMRI WB and ROI	overt picture naming	9/12 (75%)	↑ activation for treated language (L2) bilaterally; more extensive activation for L2 than L1 post-tx (whereas activation was similar pre-treatment for both languages). Activation was noted in language areas, and extended anteriorly to exective control areas (bilateral prefrontal cortex). DCM analysis of 5 LH ROIs (L ITG, L IFGtri, L IFGorb, L caudate, ACC) shows ↑ global connection strength/coupling for L2 (not L1) between all specified ROIs in LH naming and executive control regions
Benjamin, et al., 2014	Parallel cohorts	13	Naming + category generation IT (with complex left-hand movement) vs. CT (no left-hand movement)	er-fMRI ROI	overt category member generation	8/17 (47%)	Significant rightward shift in lateral frontal activity pre- to post-treatment (and at 3-month follow-up) for IT but not CT condition. Rightward shift in posterior perisylvian activity during category member generation was significantly correlated with treatment gains in IT (but not CT) condition.
Crosson, et al., 2009	Case-control, MB AB crossover	5	IT (naming + complex L hand movement	er-fMRI ROI	overt category member generation	10/17 (59%)	↓ R and L lateral frontal activation was noted for 3/4 individuals who improved in therapy, while the remaining individual showed ↑ R lateral frontal activity post-treatment . Overall, activation post-treatment appeared increasingly concentrated in the right lateral frontal cortex (i.e., motor + premotor cortices), suggesting increased neural efficiency induced by therapy. Posterior perisylvian activity remained the same or greater in the LH for those who improved in therapy. Treatment responders showed a significant rightward shift in lateral frontal activity pre- to post-therapy. Compared to controls, this right lateralization was significantly greater post- (but not pre-) treatment. For the non-responder, a significant leftward shift in lateral frontal activity was observed. No discernible laterilzation patterns were seen for activity in the medial frontal or posterior perisylvian cortices across cases.
Davis, et al., 2006	Case study	1	Intensive computerized semantic decision-making and categorization	fMRI-block ROI	covert lexical decision verb generation text listening	7/14 (50%)	For the verb generation task, ↑ activation was noted in L IFG and L DLPFC post-therapy. ↑ activation was also noted in RH lesion homologue associated with semantic route to word retrieval (R occipital-temporal junction). ↓ activation was noted in primary visual areas. For text listening (auditory comprehension) task, ↑ activation was noted in temporoparietal ROI (L SMG, L IPL, L MTG, L STG) post-therapy, with a corresponding↓ in activation of RH areas. No changes in activation for lexical decision task. Strong leftward shift in temporoparietal ROI (L SMG, L IPL, L MTG, L STG) for the text listening task post-treatment, which corresponded to improved auditory comprehension.
Della Rosa, et al., 2014	Case-series	2	Progressive syllabic cueing	er-fMRI WB and ROI	overt picture naming	11/13 (85%)	↑ activation in L IFG (crossed subcortical aphasia) and R IFG (subcortical aphasia) were associated with improved naming performance post-treatment. Thus, functional recovery was mediated predominantly by recruitment of lesion homologue areas, regardless of lesion lateralization.
Durand, et al., 2021 *[merge with Durand et al., 2018]*	Cohort-control (2021) Case-series (2018)	2	POEM (verb naming, with gesture and visualization)	er-fMRI WB (2018 paper)	overt picture (noun) and video (verb) naming	9/13 (69%) [2021] 11/16 (69%) [2018]	No direct pre-post comparisons were made. Post-therapy, naming of trained items activated L cerebellum, bilateral MTG, R fusiform and R premotor cortex. Overall, fewer brain regions were recruited post-therapy.Post-treatment, one case demonstrated an increase in predominantly LH activation for treated words, and a shift to predominantly RH activation for untreated words. The other case demonstrated a shift to predominantly RH activation for treated words only; no suprathreshold clusters were notetd for the untreated words.

Fridriksson, et al., 2012 *[merge with Fridriksson, et al., 2010]*	Parallel alternating cohorts	29	Semantic and phonological cueing (alternating)	er-fMRI WB and VOI	overt picture naming	13/16 (81%) [2012] 14/16 (88%) [2010]	↑ activation in LH perilesional frontal lobe areas was the strongest predictor of improvements in naming accuracy. ↑ activation in residual temporal lobe language network was the strongest predictor of reduced semantic paraphasias. ↑ activation in residual temporoparietal language network was the strongest predictor of reduced phonemic paraphasias.
Fridriksson, et al., 2006	SSMB	3	Group therapy: intensive hierarchical cueing (errorless approach: word repetition, phonemic cueing, naming)	er-fMRI WB	overt picture naming	13/14 (93%)	P1: ↑ activation in L temporal pole (i.e., perilesional) and R inferior parietal lobe (homologuous) pre- to post-treatment. P3: ↑ activation in phonological processing area (L parietal lobe, posterior to lesion), frontal poles, and anterior cingulate gyrus pre- to post-treatment. P2: fMRI analysis was not possible due to extensive inferior frontal lobe WM damage (i.e., disconnection with residual cortex) and minimal response to treatment.
Johnson, et al., 2019 *[merge with Johnson et al., 2021 and Braun et al., 2022]*	Cohort-control	26 (treated) 10 (untreated)	Semantic categorization, decision-making, feature-matching, and generative naming	er-fMRI ROI	overt picture naming	10/16 (63%) [2019] 11/16 (69%) [2021] 8/12 (67%) {2022]	Overall, treatment responders showed significantly↑ activation of the RH compared to the LH after therapy. Post-treatment, there was an overall ↑in activation when averaged across all ROIs. Non-responders and untreated people with aphasia showed virtually no changes in activation after therapy. Therapy may upregulate traditional language areas and RH homologues: compared to healthy controls, individuals with aphasia showed ↑ activation in bilateral IFG and R MFG post-treatment.
Kiran, et al., 2015	Single-subject design with HC group	8	SFA and semantic decision-making	er-fMRI VOI	overt picture naming semantic verification	10/16 (63%)	Findings suggest that rehabilitation re-engages core language processing regions (i.e., as seen in healthy controls). Post-treatment, significantly ↑ activation was noted for 2-3/8 participants, in R IFG, R SFG, L MFG and L MTG for picture naming, and in L PCG, R SFG and R MFG for semantic verification. Of those, the most commonly activated regions exceeding uncorrected thresholds post-treatment (i.e., for > 7/8 participants) were the L MFG for naming and the R MFG for semantic verification. DCM effective connectivity analysis shows L IFG to be the most consistently activated and modulated region post-treatment, followed by R IFG and L MFG, independent of task. In addition, post-treatment modulation of the L SFG, L ITG, and L fusiform was seen in the naming task, and of the R MFG and bilateral MTG in the semantic verification task.
Kurland, et al., 2010	SSMB AB design	1	CILT then PACE (for object and action naming)	fMRI-block WB	overt picture naming	10/12 (83%)	Pre-treatment scan data not available. Picture naming activated L frontal network (L MFG, L IFG, L SMA and L pre-SMA), regardless of treatment (CILT, PACE) and stimulus type (correctly named, trained, untrained, incorrectly named). This L frontal network, thought to support response selection, self-monitoring and inhibition, was least active during accurate naming (i.e., of known and/or trained items), and most active during incorrect (i.e., effortful) naming.
Leonard, et al., 2015	Case-series	2	PCA - Choice vs. No Choice conditions	fMRI-block WB LV PLS analysis	covert semantic and rhyme judgments	6/11 (55%)	Although behavioural improvements were noted in both participants, only P2 (with larger treatment effect) demonstrated associated neural changes. Namely, ↑ activation was noted in bilateral PFC, R thalamus, R middle occipital gyrus and R precuneus for the phonological rhyme judgment task; ↑ activation was noted in bilateral PFC, L cingulate, L MTG and R insula for the semantic judgment task.
Marcotte, et al., 2013 *[merge with Marcotte, et al., 2012]*	Cohort-control	9	SFA	fMRI-block WB	overt picture naming	8/13 (62%) [2013] 11/16 (69%) [2012]	In those with the greatest response to treatment, ↓ overall activation was observed post therapy, whereas less successful responders showed ↑ overall activation. Post-treatment, naming activated L IPL, a semantic integration area. Post-treatment, activation of the L precentral gyrus was significantly correlated with naming improvement. Damage to Broca's area was associated with poorer treatment gains. Spatial ICA analyses of functional connectivity (FC) show significant modulation of the posterior default-mode subnetwork following treatment (which notably includes the precuneus). No significant correlations found between this increase in FC and naming improvement post-treatment, although trends in the data suggest that greater pre-treatment integration of the default-mode network may lead to greater treatment success.

Marcotte & Ansaldo, 2010	Case study	1	SFA (nouns and verbs)	er-fMRI WB	overt picture naming	5/14 (36%)	Pre-treatment, greater activation noted in RH regions. Post-treatment, fewer brain regions recruited overall, however reactivation of LH perllesional naming-specific areas was seen post-treatment.
Meinzer, et al., 2008	Case-series	11	CIAT	fMRI-block ROI (defined by MEG)	overt picture naming	5/11 (45%)	MEG was used to determine areas of dysfunctional slow wave (delta) activity in each individual's perilesional cortex (i.e., delta ROIs). Post-treatment activation ↑ in individual LH perilesional delta ROIs was significantly correlated with improved naming of treated words. Activation ↑ was also noted in ipsilesional ROIs more distant from the lesion, and in RH homologues of LH ROIs, however these were not correlated to naming improvements.
Meinzer, et al., 2007	Case study	1	CIAT (in L2, German)	fMRI-block WB	overt picture naming	5/9 (56%)	Activation ↑ noted post-treatment in bilateral fronto-temporal regions for items named in treated language (German). No differences in activation were noted for items named in untreated language (French).
Meinzer, et al., 2006	Case-control study	1	CIAT	fMRI-block WB	overt picture naming	7/12 (58%)	Pre- to post-treatment, ↑ activation was noted in R IFG, R thalamus, R ACC and bilateral putamen. ↑ activation in R IFG was associated with correct naming (but not with the production of paraphasias or neologisms)
Nardo, et al., 2017	Cohort	18	Computerized error-reducing phonological cueing (whole word, initial phoneme)	er-fMRI WB	overt picture naming cued picture naming	9/14 (64%)	A neural priming effect (i.e., decreased activation) was seen for treated items following therapy (R anterior insula, bilateral IFG and ACC, L premotor). A greater ↓ in activation in R frontal regions post therapy was correlated with the greatest improvements in naming reaction times. ↑ activation was seen in the precuneus and ACC during naming of treated (compared to untreated) words post-therapy. Whole-word cues activated R AG; partial word cues activated L SMA, R anterior insula, R IFG, and R BG.
Peck, et al., 2004	SSMB with matched controls	3	IT (naming + complex L hand movement) vs. AT (naming stimuli presented in left hemispace)	er-fMRI ROI time to peak (TTP) analysis	overt category member generation	9/14 (64%)	Both behavioural and neural response times got faster post-therapy, closer to values posted by controls. Timing delay (between auditory input and verbal response) was signifcantly correlated to TTP. Two individuals (one in each condition) showed decreased TTP (faster neural reponding) pre- to post-treatment in RH Broca's homologue, motor cortex and pre-SMA. The third individual showed decreased TTP pre-to-post treatment in RH pre-SMA, but ↑ TTP pre- to post-treatment in R Broca's homologue, motor cortex, and auditory cortex.
Rochon, et al., 2010	SSMB	2 (treated) 2 (untreated)	PCA	fMRI-block WB LV PLS analysis	covert semantic and rhyme judgments	6/13 (46%)	Overall, both treated patients showed a greater number of LH (vs. RH) activations post-treatment primarily for the semantic task (↑ activation in L IFG, L MTG, L SMG, L cuneus, bilateral IPL, and R precuneus). In contrast, untreated patients showed an equal or greater number of significant activations in the RH (vs. LH).
Truzman et al., 2021 [merge with Rochon et al., 2010 and Leonard et al., 2015] *[case-series]*	Case-series	4	PCA	fMRI-block VOI	covert semantic and rhyme judgments	8/13 (62%)	Overall, DCM effective connectivity analysis of VOIs in the RH (R dorsal IFG, R ventral IFG and R lateral temporal cortex), reveal normalization of connectivity following treatment (i.e., becoming more similar to healthy controls). Namely, there was an ↑ in connectivity between the R lateral temporal and R ventral IFG regions in the phonological task, and in the R lateral temporal region in the semantic task. In addition, an increase in connectivity was noted between the R lateral temporal and R dorsal IFG regions for the phonological task, beyond that seen in healthy controls, suggesting that this change in connectivity reflects compensatory reorganization processes. No significant changes were noted for the semantic task.
Vitali, et al., 2010 *[merge with Vitali et al., 2007]*	SSMB	1	Progressive syllabic cueing	er-fMRI WB (from 2007 paper)	overt picture naming	7/12 (58%) [2010] 7/14 (50%) [2007]	Post-treatment, ↑ activation was seen mainly in RH lesion homologues (R IFGtri) in a patient with a completely lesioned Broca's area. Additional post-treatment activations were noted in the L SMG, L MFG, L SFG, R precuneus, and R posterior cingulate. Overall, ↑ BOLD effective connectivity was observed among RH ROIs (between IPL bilaterally, R MTG and R IFG) for naming of trained items, and among LH ROIs (between L MTG and L IPL) for untrained items.

Note: ACC – anterior cingulate cortex; AG – angular gyrus; AT - Attention Treatment; BG – basal ganglia; CIAT – Constraint-Induced Aphasia Therapy; CILT - Constraint-Induced Language Therapy; CT - Control Treatment; DCM - Dynamic Causal Modeling; DLPFC – dorsolateral prefrontal cortex; er - event-related; fMRI - functional Magnetic Resonance Imaging; HC - healthy control; ICA - Independent Components Analysis; IFG - Inferior Frontal Gyrus; IPL – inferior parietal lobule; IT - Intention Treatment; ITG – inferior temporal gyrus; L - Left; L1 – First language; L2 – Second Language; LH - Left hemisphere; LV PLS – Latent variable partial least squares; MB – Multiple baseline; MEG – Magnetoencephalography; MFG – middle frontal gyrus; MTG – middle temporal gyrus; NA - Not applicable; PACE - Promoting Aphasic's Communicative Effectiveness; PCA - Phonological Components Analysis; PCG – precentral gyrus; PFC – prefrontal cortex; POEM - Personalized observation, execution, and mental imagery therapy; R - Right; ROI: region of interest; SFA - Semantic Feature Analysis; SMG – supramarginal gyrus; SFG – superior frontal gyrus; SMA – supplementary motor area; SSMB - Single subject multiple baseline; STG – superior temporal gyrus; TTP – time-to-peak; VOI - voxel of interest; WB - whole-brain; WM – white matter.