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Plasticity of Sentence Processing Networks: Evidence from a patient with agrammatic variant of Primary Progressive Aphasia (PPA)

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Abstract

This study reports the results of a longitudinal study examining the effects of treatment for sentence processing deficits for a 70-year-old gentleman (DK) with the agrammatic variant of Primary Progressive Aphasia (PPA). On entry into the study, he presented with a 2-year history of impaired verb and sentence processing and concomitant neural atrophy in primarily subcortical regions. Spanning an 18-month period, treatment focused on improving comprehension and production of syntactically complex, passive and object cleft, structures, consecutively. Results, derived from extensive behavioral and neurocognitive testing, showed not only improved ability to comprehend and produce both trained and untrained, less complex, linguistically related structures in offline tasks, but also improved online sentence processing strategies as revealed by partially normalized eye movements in online comprehension (i.e., emergence of thematic prediction and thematic integration) and production (i.e., use of incremental processing) tasks. Changes in neural activation from pre- to post-treatment of both structures also were found, with upregulation of tissue in both the left and right hemispheres, overlapping with regions recruited by neurotypical adults performing the same task. These findings indicate that Treatment of Underlying Forms (TUF) is effective for treatment of patients with the agrammatic variant of PPA (as it is for those with stroke-induced agrammatism), and show that unaffected neural tissue in patients with PPA is malleable and may be recruited to support language, providing evidence of experience-based plasticity in neurodegenerative disease.

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Disclosure of interest

The authors report no conflict of interest.

Keywords

neural plasticity; Primary Progressive Aphasia (PPA); agrammatic variant of PPA; Treatment of Underlying Forms (TUF); Wh-movement structures; NP-movement structures; eyetracking; visual world paradigms; functional neuroimaging

Introduction

Research examining the effects of language treatment in patients with primary progressive aphasia (PPA) has shown that behavioral intervention results in improved language ability. As shown in Table 1, which provides a review of 26 studies, including 131 participants across studies, most studies have focused on improving noun (or verb) naming (15 studies), and only one has directed treatment toward improving sentence-level deficits in PPA (Hameister, Nickels, Abel, & Croot, 2017). A few studies have also shown changes in neural processing resulting from treatment. Beeson et al. (2011) reported increased activation from pre- to post-naming treatment for a patient with logopenic PPA in the left dorsolateral prefrontal region using functional magnetic resonance imaging (fMRI). Another study, using anodal transcranial direct current stimulation (tDCS) applied to the left inferior frontal gyrus and posterior perisylvian regions in a patient with the nonfluent variant of PPA (nfvPPA), reported changes associated with language improvement in approximate entropy (measured by EEG recordings during a repetition task) in left Broca's and bilateral Wernicke's areas (Wang, Wu, Chen, Yuan, & Zhang, 2013). Bonakdarpour, Basu, Grasso, Schnyer, and Henry (2018) also found increased resting-state activity in left posterior perisylvian and bilateral anterior cortical regions in four participants with nfvPPA after 4–6 weeks of Video-Implemented Script Training for Aphasia (VISTA, Henry et al., 2018). These findings suggest that improvements in language ability in PPA are possible and that non-atrophic regions of the brain are sufficiently malleable to be recruited to support language.

Neuroplasticity is now recognized as a basic principle of cognitive neuroscience in that the human brain continues to create new neural pathways and alter existing ones as a result of experience and learning throughout the lifespan and following damage to the brain (e.g., stroke) (Kerr, Cheng, & Jones, 2011). A relatively large literature has emerged in stroke aphasia, showing that treatment-induced language improvement is associated with changes in neural activation patterns (see Kiran & Thompson, 2019, for a review). As in the PPA literature, most studies have focused on improving naming (e.g., Fridriksson, Richardson, Fillmore, & Cai, 2012; Kiran, Meier, Kapse, & Glynn, 2015), however, a few have also shown that sentence processing treatment improves both offline and online processing in people with aphasia and that these changes correlate with shifts in neural activation within regions supporting sentence processing and domain-general neural networks, even in patients with chronic aphasia (Barbieri, Mack, Chiappetta, Europa, & Thompson, 2019; Mack & Thompson, 2017; Mack, Nerantzini, & Thompson, 2017).

Still controversial in the stroke aphasia literature is whether left and/or right hemisphere regions are the best candidates for recruitment into the language network. This literature indicates that both are viable, although the regions recruited depend on several factors, including organism-internal (i.e., lesion related) and external (i.e., treatment and other

environmental factors) variables (Kiran & Thompson, 2019). Similarly, it is likely that the neural tissue recruited to support language improvement in PPA is influenced by at least some of these factors (Bonakdarpour et al., 2018; Catani et al., 2013).

The present study examined the neurocognitive effects of treatment for sentence production and comprehension in one patient (DK) with the agrammatic variant of PPA (PPA-G) (Gorno-Tempini et al., 2011; Mesulam et al., 2009). DK presented with relatively spared word and sentence comprehension and semantic knowledge, and impaired verb and sentence production. Given this, the patient was enrolled in Treatment of Underlying Forms (TUF; Thompson & Shapiro, 2005), a metalinguistic intervention that has been shown to improve sentence processing in patients with stroke agrammatic aphasia (Thompson, 2019). Prior to and following treatment, we used eyetracking to chart changes in on-line sentence processing and fMRI to examine changes in neural activation. We predicted that treatment would improve processing of trained sentence structures and, based on the Complexity Account of Treatment Efficacy (CATE; Thompson, Shapiro, Kiran, & Sobecks, 2003), generalization to simpler, linguistically-related structures would occur. Also, as in stroke agrammatic aphasia, we predicted that treatment would impact on-line sentence processing strategies and that treatment-induced improvements would be associated with bilateral increases in BOLD signal activation, in regions overlapping with those engaged by healthy people.

Method

Participant

DK, a 70-year-old Caucasian, monolingual English-speaking, right-handed male, clinically diagnosed with PPA served as the participant in this study. Neurological examination indicated no evidence of stroke, tumor or history of neurological, psychiatric, or developmental speech, language, or learning impairments, and he showed normal hearing and corrected-to-normal vision. At study onset, he reported a two-year history of progressive language decline. As indicated in Table 2, upon study entry, DK's comprehension of single words (nouns and verbs) was at ceiling, whereas, mild difficulties were noted in comprehension of non-canonical (and not canonical) sentences. Verb production showed a graded impairment according to verb argument structure complexity, and difficulties were noted in production of both canonical and non-canonical sentences. Narrative speech was characterized by production of short, often ungrammatical, sentences, with errors in production of verb argument structure and verb morphology. No evidence of motor speech deficits was found, and overall, language patterns were consistent with the agrammatic variant of PPA (PPA-G; Gorno-Tempini et al., 2011; Mesulam et al., 2009). Administration of the *Western Aphasia Battery-Revised* (WAB-R; Kertesz, 2007) indicated an Aphasia Quotient (AQ) of 71.0, whereas memory, attention, executive function, abstract reasoning and conceptual flexibility test scores were within the average to very superior range. The study was approved by the Northwestern University Institutional Review Board (IRB). DK and four groups of healthy control participants, who participated in the structural (VBM) and functional (fMRI) neuroimaging, and in the active/passive and object cleft/subject cleft

eye-tracking portions of the study, met MRI safety criteria and provided written informed consent according to IRB policies.

Sentence Structures and Stimuli

Sentence types used for training included long passives and object-cleft structures. Generalization to untrained linguistically-related short passives, active sentences with unaccusative or transitive verbs, and linguistically-unrelated cleft structures were tested during passive sentence training. During object cleft treatment, untrained object Wh-questions, and unrelated pronominal structures and passives were tested (see Table 3).

For all sentence types, except actives with unaccusatives, sentence/picture pairs with semantically reversible participant roles and transitive verbs were developed (n=20 each). Unaccusative intransitive verbs were non-alternating and selected for animate (Theme) arguments, with corresponding pictures depicting the same action performed by participants of the opposite sex. Unaccusative and transitive verbs were matched for length in syllables, frequency of usage as a verb based on the Corpus of Contemporary American English, and imageability based on the MRC database (Coltheart, 1981). The same six nouns were used as verb arguments across structures. Materials for training sentences (1) and (5) included word cards for the Action (in both the active and passive/object cleft form), Agent, Theme, and Location, as well as two sentence templates (one for the active and one for passive/object cleft forms).

Design

A longitudinal single-subject multiple-probe design was used to evaluate the effects of treatment. Following baseline testing (two consecutive probes), passive structures were trained, followed by repeat testing of all structures immediately following, six months, and one-year post treatment. Object-cleft structures then were trained after pre-treatment testing (three consecutive probe sessions), followed by post-testing of both structures immediately following and six months post-treatment. Both training periods spanned 12 weeks each (1.5-hour sessions; twice weekly). Sentence comprehension and production probe tasks (see Barbieri et al., 2019, for details) were administered throughout both training periods to evaluate the acquisition and generalization effects of treatment. Online eyetracking and neuroimaging data also were collected prior to and following each training period.

Two visual-world eyetracking tasks were administered prior to and following passive sentence treatment, using an ASL EYE-TRAC 6000 remote eye- tracker (Applied Science Laboratories, Bedford, MA), to test online processing of passive and active sentences. These included a sentence-picture matching task to evaluate on-line comprehension (after Mack and Thompson (2017)) and a syntactic priming task to evaluate production (after Mack et al., 2017). There was no overlap between the verbs/sentences used in training and the stimuli used for eyetracking. Prior to and following object cleft treatment, a sentence-picture matching task also was used to test online comprehension of object (e.g., *It was the woman who the man lifted*) and subject clefts (e.g., *It was the man who lifted the woman*). The verbs and nouns were the same as those used in the passive vs active task.

Brain images were acquired before and after each treatment phase using a Siemens 3T Prisma scanner, 64-channel head coil and echo-planar sequences for anatomical (3D MPRAGE, TR=2300ms; TE=2.91ms; flip angle=9°, FOV=256mm; voxel size=1×1×1mm) and functional (TR=2400ms; TE=20ms; flip angle=90°; FOV=220mm; voxel size=1.7×1.7×3mm) scans. Block-design fMRI picture-verification tasks (as in Europa, Kiran, Gitelman, & Thompson, 2019) were used to evaluate comprehension of (1) passive and active sentences, and (2) object-cleft and subject-cleft sentences, both running in E-Prime 2.0. Briefly, participants were presented with a picture, together with an auditory sentence, and were asked to determine if the two matched or not by pressing a button; to control for basic auditory and visual processes, a control condition consisting of scrambled pictures and digitally reversed speech was also included.

Treatment (TUF)

Both passive and object-cleft structures were trained using TUF. This approach uses a set of metalinguistic steps that emphasize the argument structure of verbs and thematic/syntactic mapping from canonical (active) to noncanonical forms (see Thompson, 2019).

Data analyses

Offline Probe Data—Performance on the weekly probe tasks was plotted over time to show acquisition of trained and untrained structures. We also calculated the mean percentage correct responses on baseline and post-treatment probes to calculate effect size (ES) using Cohen's H formula.

Online Eyetracking Data—The eye data were analyzed by tallying fixations (i.e., a gaze of at least 100ms within one degree of visual angle) within areas of interest – for the target and foil pictures in the sentence-picture matching task and within rectangles surrounding the Agent and Theme for the syntactic priming task – using EYENAL (Applied Science Laboratories) and Data Viewer (SR Research Ltd). For sentence-picture matching tasks, data were aggregated into 50ms bins and time-locked to the onset of the picture + auditory sentence pair. For both tasks, data from groups of healthy controls were used for data analysis (n=10 for passive/active sentence-picture matching (from Mack & Thompson, 2017); n=12 for active/passive syntactic priming (from Mack et al., 2017); for object/subject relative sentence-picture matching n=6 participants were tested). Sentences were split into regions: for passive sentences (e.g., *the woman was lifted by the man*): noun 1 (NP1), verb, (V), noun 2 (NP2), and the first 1000ms following sentence end (S End); for object clefts (e.g., *It was the man who the woman was lifting*): NP1, NP2, V and S End regions. *Thematic prediction* (TP) and *thematic integration* (TI) scores were calculated, reflecting fixations during NP1 and NP2, respectively, and 1000ms after sentence end. In normal sentence processing, the proportion of fixations to the target picture during NP1 is low (<0.5), reflecting TP (i.e., prediction of an Agent thematic role, resulting in looks to the distractor picture for passive and object-cleft sentences), and high (>0.9) during NP2 and downstream, reflecting successful TI (i.e., correct thematic role assignment, resulting in looks to the target picture). Scores for DK were compared to those derived from healthy adults performing the same tasks, using Wilcoxon signed-rank tests.

For syntactic priming, 100 ms bins time-locked to the onset of target pictures were used to calculate the proportion of fixations to the Agent and Theme for each trial and sentence region (Onset, PreNP1, NP1, V, NP2, S End). These data were binarized: Agent advantage = greater fixations to the Agent; Theme advantage = greater fixations to the Theme.

Neuroimaging

Structural.: Anatomical scans, collected prior to each treatment period, were pre-processed using a custom-made pipeline (including re-orientation to the AC-PC line; segmentation; normalization to the VBM/DARTEL template), available through the Northwestern University Neuroimaging Data Archive (NUNDA). Modulated gray-matter maps for DK and a group of healthy controls (n=76; Age = 63.6±7.4, range: 50–80, scanned as part of two other projects (NIH-P50DC012283 and NIH-R01DC008552, using the same parameters) were thresholded at 20% intensity and entered into non-parametric Voxel-Based Morphometry (VBM) analysis (using SPM, Statistical Non-Parametric Mapping toolbox (SnPM, version 13.1.06, http://www.nisox.org/Software/SnPM13/) (see Scarpazza et al., 2016). Briefly, pseudo-t maps reflecting the differences in the amount of gray matter between DK and the control group were obtained by perfoming voxel-wise permutations of conditions (N=77, resulting in a smallest possible voxel-wise p-value of p=.013) with smoothed variance of 4×4×4mm, and thresholded using a cluster-level threshold of p<.001 (FWE p<.05 correction).

FMRI.—Pre-processing used the NUNDA RobustfMRI pipeline, with the same parameters as in Barbieri et al. (2019); motion correction regressed out volumes with FD (framewise displacement)>0.9mm. Fixed-effect General Linear Model (GLM) voxelwise analyses used SPM12 to determine activation for *passive>control* and *object-cleft>control* conditions at pre and post-treatment, as well for post>pre-treatment. Analyses were restricted to a set of brain regions that support sentence processing in healthy participants (see Walenski, Europa, Caplan, & Thompson, 2019), including the following (bilateral) regions: the inferior frontal gyrus (IFG), frontal operculum, insula, middle frontal gyrus (MFG), precentral gyrus (PCG), temporal pole, inferior temporal (ITG), middle temporal (MTG), and superior temporal gyri (STG), supramarginal gyrus (SMG) and angular gyrus (AG). For analyses of DK's data, time and dispersion derivatives were introduced in the model to account for delayed hemodynamic response (Rombouts, Goekoop, Stam, Barkhof, & Scheltens, 2005) and T-maps were thresholded at p(unc.)<.001, with cluster-level FWE (p<.05) correction. For healthy individuals (N=23), second-level analyses were conducted using one-sample t-tests, with age as a covariate. Group T-maps were thresholded at p(unc.)<.001, with cluster size determined using AFNI's 3dClustsim, a permutating testing function which simulates noise volumes to determine an appropriate cluster size to achieve FWE threshold of p<.05.

Results

Treatment Effects

Performance on Treatment Probe Tasks—Weekly probe data (Figure 1, top) showed improved production of trained passives from pre- to post-testing (from 45% to 90% correct, ES=1.027); untrained passives (tested prior to and following each treatment phase) (Figure

2) also increased from 42.5% to 87.5%, both statistically significant (Table 4). Post-treatment increases in production accuracy for all passive structures were maintained at 6 months and 1-year post-passive treatment, while no significant changes in actives with unaccusative or transitive verbs, or object-cleft structures were noted.

These production patterns were maintained during the pre-object cleft multiple probe period, followed by significantly improved production of trained object clefts (from 0% to 55% correct, ES=1.671) and generalization to object wh-questions (from 10% to 40% correct) during object-cleft treatment. Improvements were largely maintained at 6 months post-treatment. Production of passive sentences also was maintained at 6 months following object-cleft treatment. No significant change in unrelated, untrained pronominal structures occurred, as expected.

Comprehension of trained and untrained passive and unaccusative structures was above chance at baseline whereas, that for object clefts was poorer (25% correct); all were unchanged throughout the passive training phase (ES=0.132; not significant) (Figure 1, bottom). Logistic regression analyses indicated no significant changes in comprehension of any sentence types (Table 4). However, comprehension of object-cleft structures improved during training, reaching 90% and decreasing to 55% correct on the post-treatment probe task, resulting in a small but significant effect size (ES=0.512). Throughout object-cleft training, comprehension of passive sentences was maintained, with no significant differences found across test points.

Longitudinal Language and Cognitive Performance

Language Measures.: Following passive treatment, improved production of grammatical sentences, nouns and verbs, verb argument structure, and verb inflection was noted both on language tests and in narrative production. Scores were largely unchanged on pre-object cleft treatment testing, with the exception that production of complex verbs and grammatical sentences showed mild decreases (Table 2). After object-cleft treatment, declines in verb (transitive>intransitive) and sentence (noncanonical>canonical), as well as in narrative production, were noted. Single-word comprehension (with the exception of complex verbs) and canonical sentence comprehension remained relatively preserved, whereas, noncanonical sentence comprehension was variable, throughout the study.

Cognitive Measures.: Results are shown in Table 5. On entry into the study, performance on non-language tests ranged from Average to Very Superior, with the exception of verbal learning memory (i.e., the Wechsler Memory Scale-Revised (WSM-R) Logical Memory (Part 1)), which showed Low Average performance (21st percentile) and further declined after passive and object-cleft treatment. Notably, DK's performance on all other measures shifted only minimally across phases of the study and remained in the Average or above range.

Online (Eyetracking) Results

Pre and Post Passive Sentence Treatment—On the sentence-picture matching task, DK's accuracy and eye movement patterns for passives were similar to healthy adults

(Figure 3 and Table 6). Evidence of *thematic prediction* (TP) was seen at pre- and post-treatment in the same region as healthy controls (N1), whereas *thematic integration* (TI) emerged during the S End region (vs. N2 in healthy), as indicated by TP and TI scores (Table 6).

For the syntactic priming (production) task, DK's accuracy was markedly impaired prior to, but improved after, passive sentence treatment (Table 6). Eye movements at pre-treatment also differed substantially from the incremental production patterns observed in neurotypical adults (Figure 4A), who showed Agent (for actives) or Theme (for passives) advantage in the PreN1 region and the reverse pattern in the N1 and V regions, indicating thematic role assignment to the sentence subject before producing it for both sentence types. For DK, pre-treatment eye movement patterns (Figure 4B) did not differ between actives and passives in any region, reflecting impaired thematic role assignment. However, eye movement patterns at post-treatment (Figure 4C) were more similar to healthy speakers: significant interactions (p's < .05) were observed between study phase (pre-, post-treatment) and sentence type in the PreN1, V, and N2 regions.

Pre and Post Object-Cleft Sentence Treatment—In the object-subject cleft eyetracking sentence-picture matching task, DK's accuracy was lower than in healthy young adults and significantly poorer for object compared to subject-cleft structures at both pre- and post-treatment (Table 6). DK's eye movements during object-cleft sentence processing are shown in Figure 5. Following, but not prior to, treatment he showed an Agent-first strategy upon hearing NP1, as reflected by a numerical (but not significant) change in *thematic prediction* (Table 6). No evidence of *thematic integration* was shown at either test point (Table 6).

Neuroimaging Results

Structural MRI—T1 images obtained from scans – prior to and following passive and object-cleft treatment – are shown in Figure 6 and the results of the VBM analyses of these data are presented in Table 7. Prior to passive sentence treatment, atrophy was constrained to the left hemisphere in the amygdala, hippocampus and anterior parahippocampal gyrus. Throughout the study, atrophy increased in these same areas and extended to left insula and temporal pole, to the left basal ganglia (caudate, putamen, and nucleus accumbens), and to the right hemisphere (including the amygdala, the anterior parahippocampal gyrus and the temporal pole) (Figure 6).

Functional MRI

Behavioral results.: Prior to treatment, DK's in-scanner comprehension accuracy for passives and object-cleft sentences was relatively good (81.2% for both). Following passive treatment, accuracy for passives increased to 89.6%, whereas, no change in comprehension of object cleft structures was observed following object-cleft treatment.

Neuroimaging results.: Regions of BOLD signal activation at pre- and post-treatment for DK are shown in Figure 7 (overlaid with neural activation derived from the control participants (n=23; age 24–64 years; M=37.1)) and coordinates/labels are provided in Tables

8 (for controls), 9 and 10 (for DK). Healthy controls showed mostly left-lateralized activation for both *Passive>Control* and *Object-Cleft>Control* contrasts, with significant clusters in the left frontal (IFG (opercularis and triangularis), MFG and PCG), posterior temporal and inferior parietal regions. A smaller cluster of activation for *Passive>Control* was also found in the right MTG temporo-occipital and AG. At baseline, DK showed activation for *Passive>Control* in the same clusters active in healthy controls (Figure 7, Table 9), with the exception that the left IFG was less extensively recruited in DK compared to healthy participants. Following passive sentence treatment, upregulation of activation (defined as increased activation from pre- to post-treatment at a voxel-wise threshold of $p<.001$, FWE $p<.05$ cluster-level correction) was observed in bilateral inferior frontal (left IFG opercularis, right IFG triangularis), right temporal (posterior and temporo-occipital MTG) and bilateral inferior parietal (posterior SMG and AG) regions. Post-treatment upregulation also was found bilaterally in the MFG and PCG. Turning to the *Object-Cleft>Control* contrast (Figure 7 and Table 10), activation patterns at baseline showed major overlap with healthy controls in the left hemisphere; in addition, activation was observed in homologous clusters in the right frontal (IFG, MFG, PCG), posterior temporal and inferior parietal (AG, pSMG) regions. Following object-cleft treatment, DK showed further, but smaller, shifts in activation, in left frontal (IFG triangularis and MFG) and right inferior parietal (SMG) regions.

Discussion

This paper examined the neurocognitive effects of treatment focused on production and comprehension of passive and object-cleft structures in a patient with the agrammatic variant of primary progressive aphasia (PPA-G). Following Treatment of Underlying Forms (TUF; Thompson & Shapiro, 2005), which exploits what is known about normal language representation and processing, DK showed improved comprehension and production of trained noncanonical sentences and generalization to untrained simpler, linguistically-related, structures, as seen in studies of treatment for stroke-induced aphasia (Thompson, 2019). Treatment-induced improvements also were largely maintained over time. These findings support the use of psycholinguistically-based treatment for sentence processing impairments in patients with PPA and provide additional support for the Complexity Account of Treatment Efficacy (CATE; Thompson et al., 2003): generalization to less complex structures occurs following treatment focused on more complex structures only when structures are linguistically related to one another. From a neural perspective, this suggests that treatment exploiting the psycholinguistic processes that underlie processing of complex forms boosts the neural circuitry that supports computation of these forms, which, in turn, supports processing of simpler, related structures.

Performance on language tests administered prior to and following treatment also reflected improved sentence processing. Improved scores on tests of verb morphology, verb-argument structure, and sentence production/comprehension, as well as improvements in spontaneous speech, were found following passive treatment; following object-cleft treatment, language test scores showed smaller improvements. However, production of complex verbs, noncanonical sentences and narratives declined following object-cleft treatment, reflecting the neurodegenerative nature of PPA. Nevertheless, comprehension/production of both

trained sentence types was maintained over time. In addition, across the 18-month period of the study, scores on tests of cognitive function remained relatively stable, and within the normal range, with the exception of performance on the WSM-R Logical Memory test, which declined from pre to post object-cleft treatment. We note, however, that the WSM-R Logical Memory test assesses verbal memory; thus decline on this test likely reflects language, rather than general cognitive decline.

Notably, the offline behavioral improvements observed were aligned with changes in online processing. On the sentence-picture matching task for passive sentences, in line with his relatively unimpaired offline passive sentence comprehension ability, DK showed evidence of intact thematic prediction at both time points, with early looks to the incorrect picture, reflecting an “Agent-first” strategy as seen in neurotypical listeners. Evidence of partially normalized, albeit delayed, thematic integration was also noted. Similarly, his online comprehension of object-cleft structures paralleled offline performance. At pre-treatment, comprehension of object-cleft structures was quite impaired as he showed no evidence of thematic prediction or integration during the object-cleft/subject-cleft sentence-picture matching task. However, following object-cleft treatment, he showed timely thematic prediction (i.e., emergence of an Agent-first strategy), albeit thematic integration was not affected by treatment.

Eye movement changes from pre- to post-treatment also were noted on the syntactic priming (production) task. While pre-treatment eye movements showed significant abnormalities, mirroring DK’s impaired ability to produce passive sentences, partially normalized production patterns (i.e., use of an incremental processing strategy, Griffin & Bock, 2000; Mack et al., 2017) were found post-treatment. These findings indicate that behavioral treatment impacted DK’s real-time, automatic language processing abilities – not merely his ability to perform offline tests of sentence comprehension/production, which may rely on the use of processing strategies such as rehearsal and/or compensatory word retrieval. That DK’s eye movements reflected partially normalized processing strategies as a result of treatment is a strong indicator of treatment efficacy, as seen in our patients with stroke-induced agrammatism (see Barbieri, et al., 2019).

One of the primary aims of this study was to determine if/how the neural network for sentence processing reorganizes with treatment in PPA-G. We hypothesized that, due to the fact that the brain is an organ of plasticity and that much, or at least some, neural tissue remains intact in patients with PPA, treatment focused on improving sentence comprehension and production would result in experienced-based plasticity – that is, changes in neural activation from pre- to post-treatment. Notably, DK’s activation on the fMRI task at baseline showed major overlap with that of healthy participants, suggesting – in line with the relatively good off-line comprehension accuracy of passive structures, and with the evidence of limited cortical atrophy – well-preserved functionality of left-hemisphere language areas. Following passive treatment, upregulation was found, in both hemispheres, in brain regions both within the normal sentence processing network and within domain-general networks, in line with the increase in comprehension accuracy of passive structures and as seen in patients with agrammatic aphasia resulting from stroke (Barbieri, et al., 2019; see also DeMarco, Wilson, Rising, Rapcsak, & Beeson, 2018). Following object-cleft

treatment, despite the change in off-line comprehension accuracy on the probe task but in line with the unchanged performance observed on the neuroimaging task, only minor changes in activation were noted, perhaps reflecting a reduction of neuroplasticity due to the progression of the disease. Notably, this observation is further supported by the smaller changes in online sentence processing observed following object cleft (compared to passive) sentence treatment.

Importantly, changes in both behavioral performance as well as brain activity were noted in the face of neural atrophy, which progressed throughout the course of the study. Of note is that DK showed atrophied tissue in regions not typically associated with PPA-G: portions of the left basal ganglia, hippocampus, and anterior parahippocampal gyrus, with the only affected cortical regions being the temporal pole, the planum polare and the anterior temporal fusiform. Over the course of the study atrophy increased in the left and spread to some of these regions in the right hemisphere. Studies on PPA-G have found peak atrophy primarily in left frontal regions, the temporoparietal junction and anterior superior temporal gyrus (Mesulam et al., 2009; Rogalski et al., 2011), with fewer reporting peak atrophy in the basal ganglia (Mandelli et al., 2016; Tetzloff et al., 2017). To our knowledge, no previous studies have identified striatal atrophy in the absence of concomitant frontal cortical pathology. However, our findings indicate that striatal atrophy alone may disrupt sentence processing. It is also possible, at least in early phases of the study, that in addition to subcortical atrophy, DK showed cortical atrophy that was not detectable. This interpretation, however, is unlikely given that atrophy within cortical regions associated with sentence processing was not seen on repeat scans obtained throughout the course of the study.

The role of the basal ganglia in language processing has been elucidated in patients with Parkinson’s disease, some of whom, in addition to characteristic motor impairments, exhibit deficits in sentence comprehension and production (Johari et al., 2019). Kotz, Frisch, Von Cramon, and Friederici (2003) also found abnormal ERP responses to sentences with verb-argument structure violations (i.e., the typical N400-P600 is lacking a P600 component) in patients with lesions within the basal ganglia, suggesting that such lesions impair temporal sequencing associated with procedural memory, which is required for processing hierarchical syntactic structure. FMRI studies with unimpaired adults have found striatal activation associated with syntactic comprehension, and models of language processing suggest that corticostriatal connections bind cortical representations of syntactic context, for example, in Broadmann’s area 47 to structure mapping representations (i.e., grammatical constructions in Broadmann’s area 44) during sentence comprehension (Dominey & Inui, 2009). Hence, it is not surprising that atrophied tissue in the basal ganglia may lead to agrammatic production and comprehension patterns in PPA as observed in our patient.

DK also showed atrophy within the hippocampal region. This observation on initial scans was somewhat surprising in that studies with both patients and cognitively healthy participants associate these regions with declarative memory and lexical learning (Tagarelli et al., 2019), rather than grammatical processes. Notably, however, increases in atrophy within the left hippocampus increased in concert with DK’s word retrieval difficulty.

Although a major strength of this study is that we were able to chart the progression of both on-line and offline sentence processing, as well as concomitant cognitive abilities, over time in a patient with the agrammatic variant of PPA, interpretation of our functional neuroimaging findings are limited in that DK did not undergo repeat scans prior to and following each treatment phase. Without repeat scans, allowing analysis of test-retest reliability of BOLD signal activation, it is possible that changes associated with the functional neuroimaging tasks may have resulted from scan-to-scan variability, rather than changes in functional activation over time. We also note that the lack of longitudinal data for healthy controls precludes the ability to rule out the possibility that changes in DK's structural scans reflected normal aging, rather than disease progression.

Conclusion

This study illuminates changes in language and neurocognitive processes in a patient with PPA-G resulting from a course of psycholinguistically-based treatment of sentence deficits. The patient showed improved comprehension/production of trained structures, generalization to untrained, related structures of lesser complexity in keeping with the Complexity Account of Treatment Efficacy (CATE; Thompson et al., 2003), the emergence of partially normalized automatic online sentence processing strategies measured by tracking eye movements; and changes in neural activation from pre- to post-treatment of both NP- and Wh-movement structures, with upregulation of tissue in both the left and right hemispheres, overlapping with regions recruited by neurotypical adults performing the same task. These results were noted in the face of increased atrophy largely in subcortical regions, providing evidence of experience-based plasticity in neurodegenerative disease, and strongly supporting provision of behavioral treatment for patients with PPA.

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

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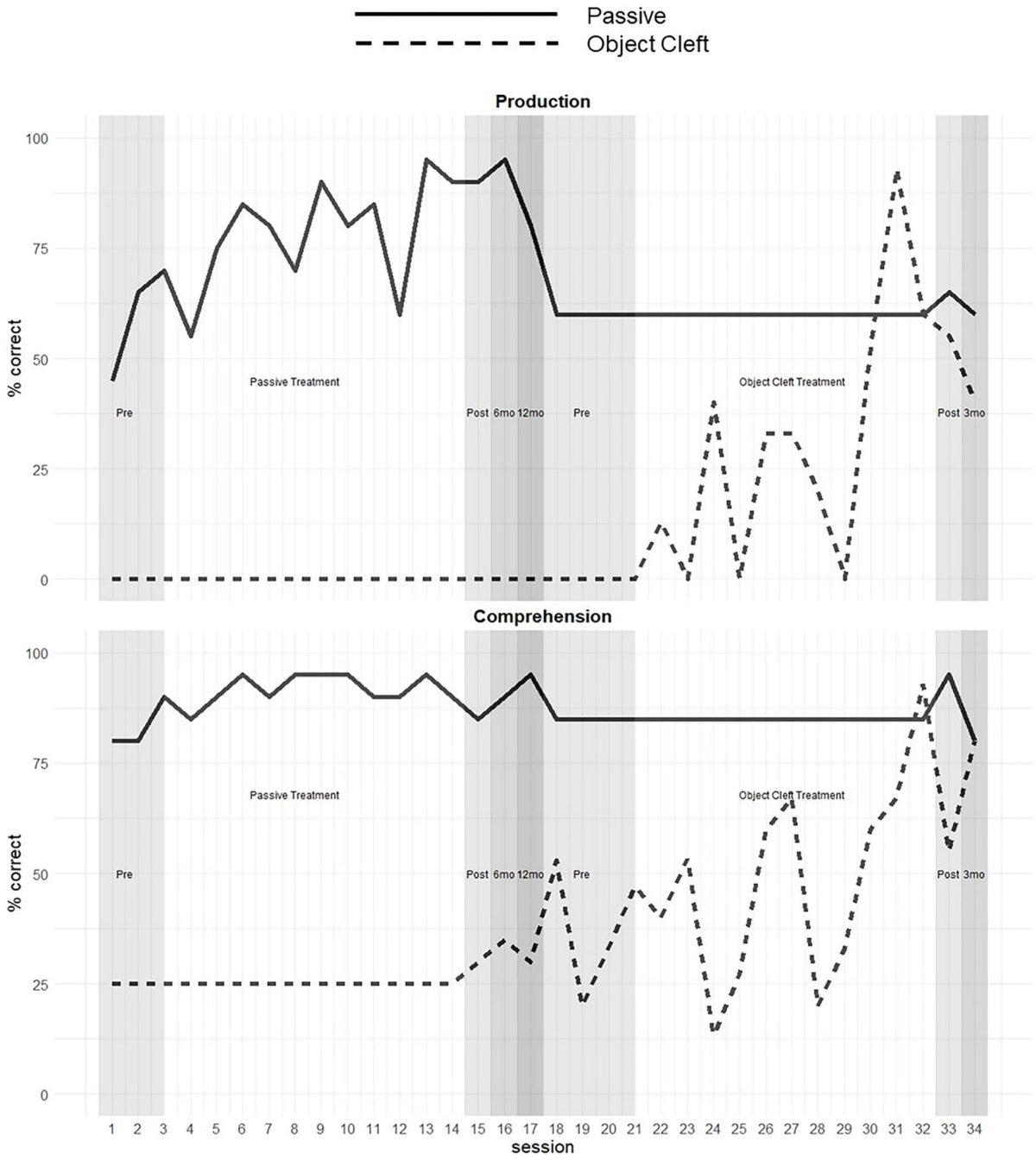

Figure 1.

Proportion of correct passive (solid line) and object cleft (dashed line) responses on production (top) and comprehension (bottom) probes administered at baseline (i.e., pre-passive training: sessions 1 and 2; pre-object cleft training: sessions 18–20), during treatment phases (passives: sessions 2 – 14; object clefts: sessions 21 – 32), and on follow-up testing immediately following passive sentence treatment (session 15), six months post passive training (session 16), 1 year post passive training (session 17), immediately

following object cleft training (session 33), and six months post object cleft training (session 34).

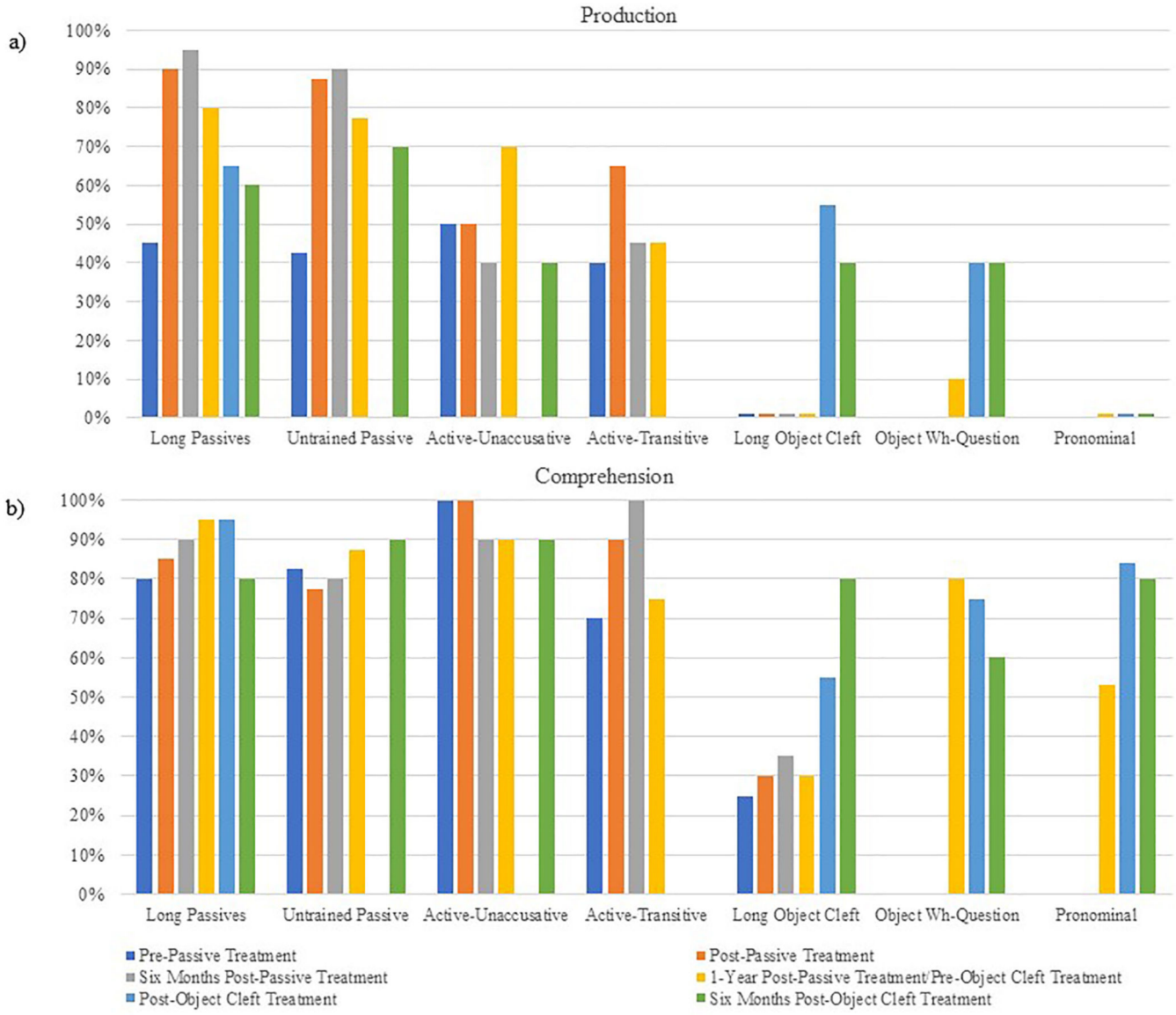

Figure 2.

Percentage correct production (a) and comprehension (b) of all sentence types across study phases.

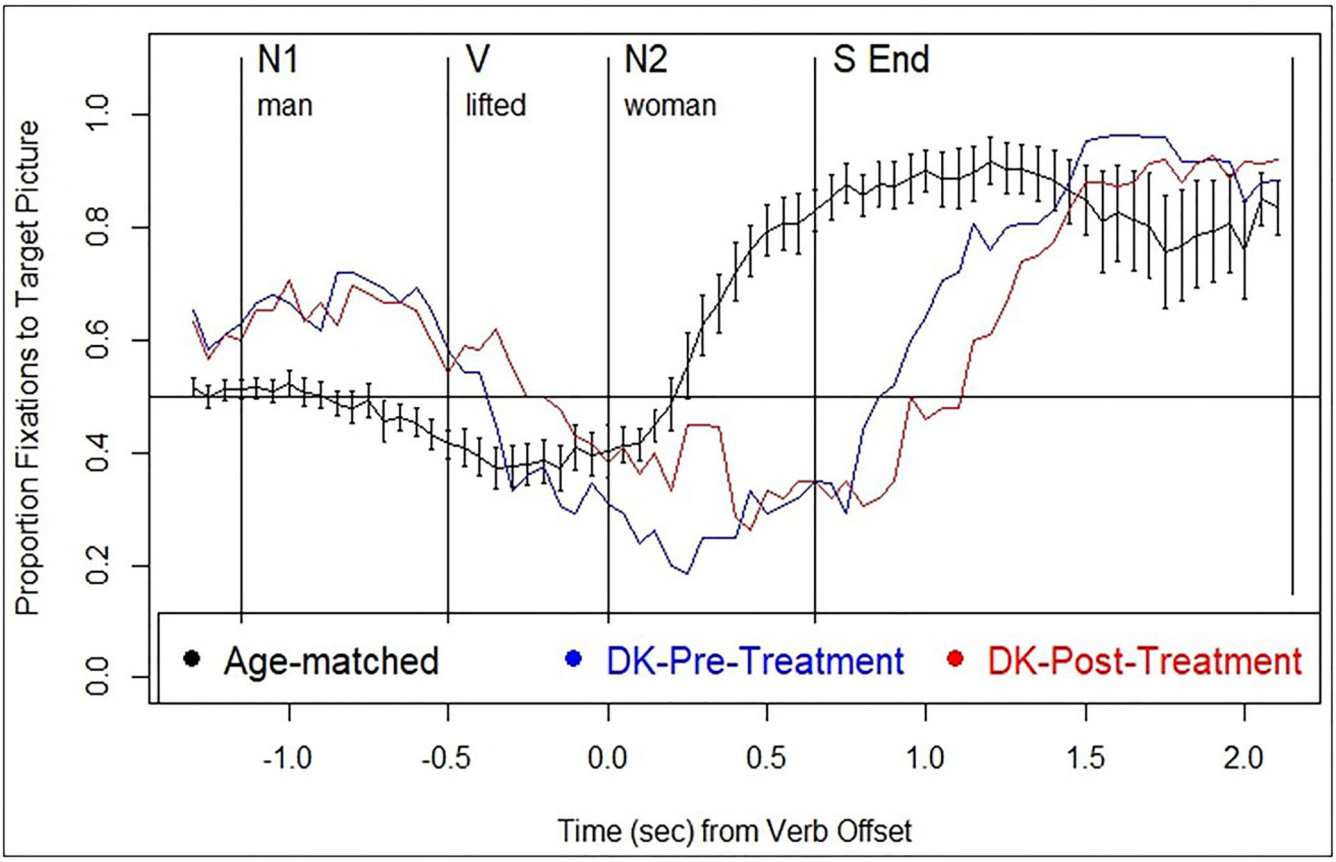

Figure 3.

Normal eye movement pattern while listening to passive sentences in the sentence-picture matching task (from Mack & Thompson, 2017) (black line) and DK's patterns at pre- (blue line) and post-treatment (red line).

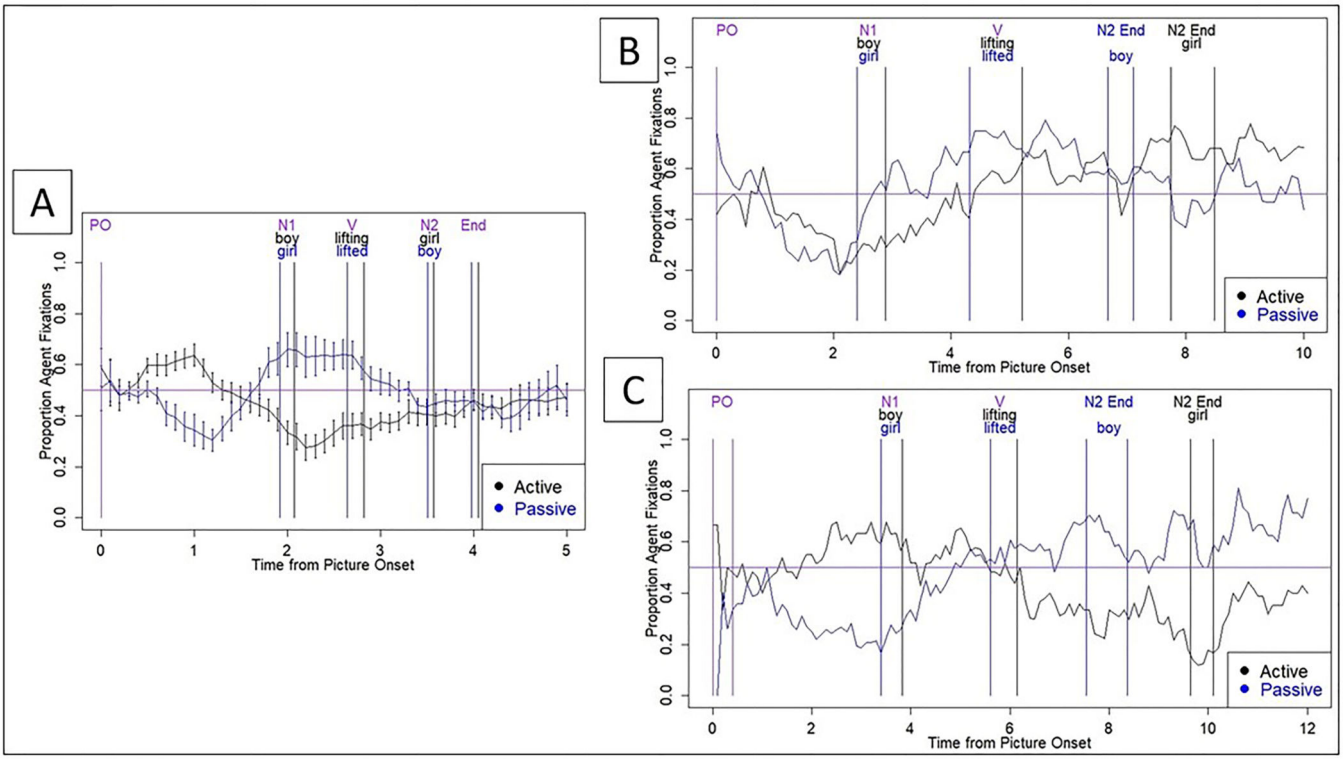

Figure 4.

Eye movements for healthy older adults (A) (from Mack et al., 2017) and DK at pre- (B) and post-treatment (C) during active (*The boy lifted the girl.)* and passive (*The girl was lifted by the boy.*) sentence production. X axis = time PO in seconds; Y axis = proportion of fixations to the agent, out of all fixations. Black line = active; blue = passive. PO = picture onset; N1 = noun 1; V = verb; N2 = noun 2; End = sentence end. The horizontal line = at-chance fixation.

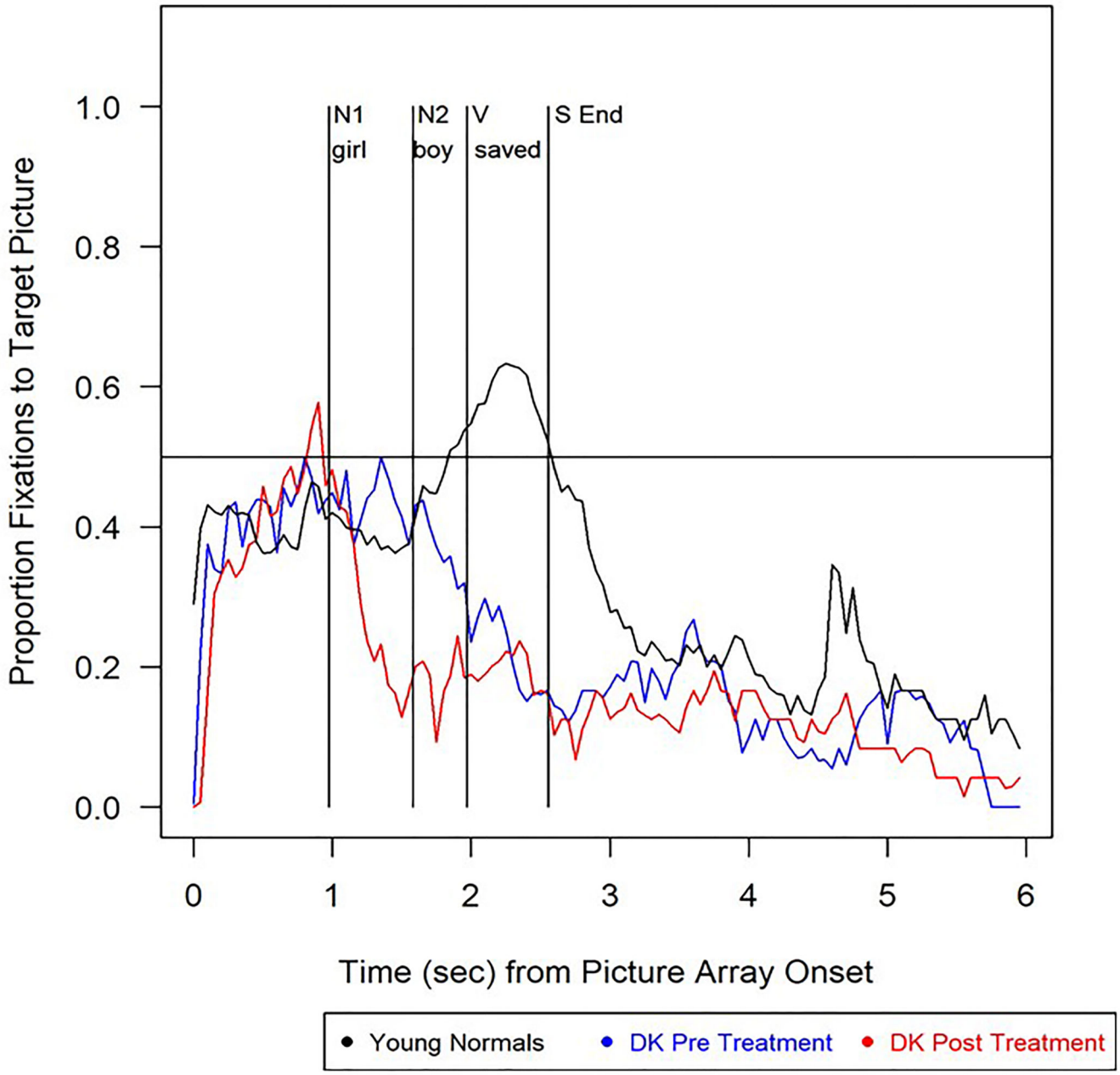

Figure 5.

Eye movement patterns while listening to object cleft sentences such as *It was the girl who the boy saved* in the object cleft sentence-picture matching task for healthy young controls (black line) and DK pre-treatment (blue line) and post-treatment (red line). Note: N1=first noun and auxiliary; V=verb; N2=second noun; S End = sentence end.

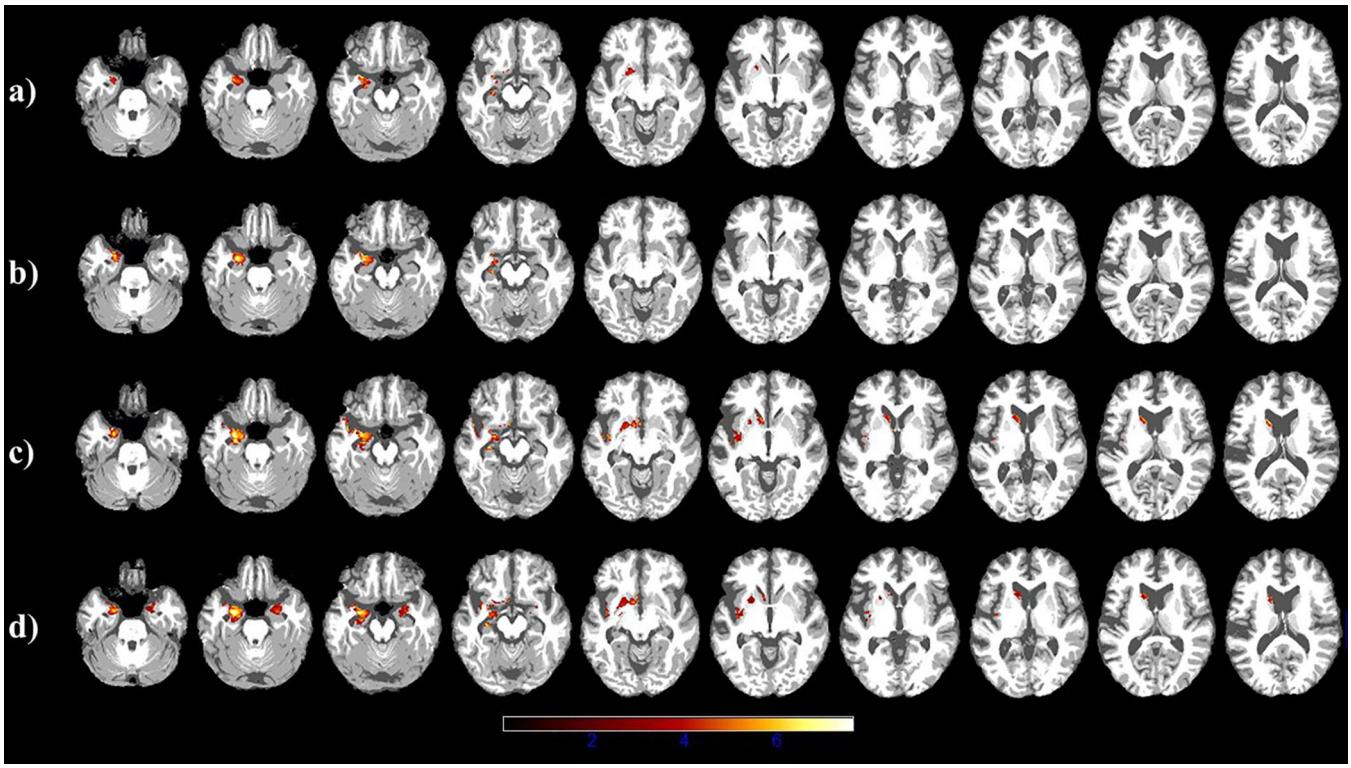

Figure 6.

Axial images showing changes in atrophy over time. Regions of significant cortical atrophy are shown prior to (a) and following (b) passive sentence treatment, and prior to (c) and following (d) object cleft treatment. Lighter colors indicate regions of greater atrophy in DK's brain compared to a group of healthy participants (N=76).

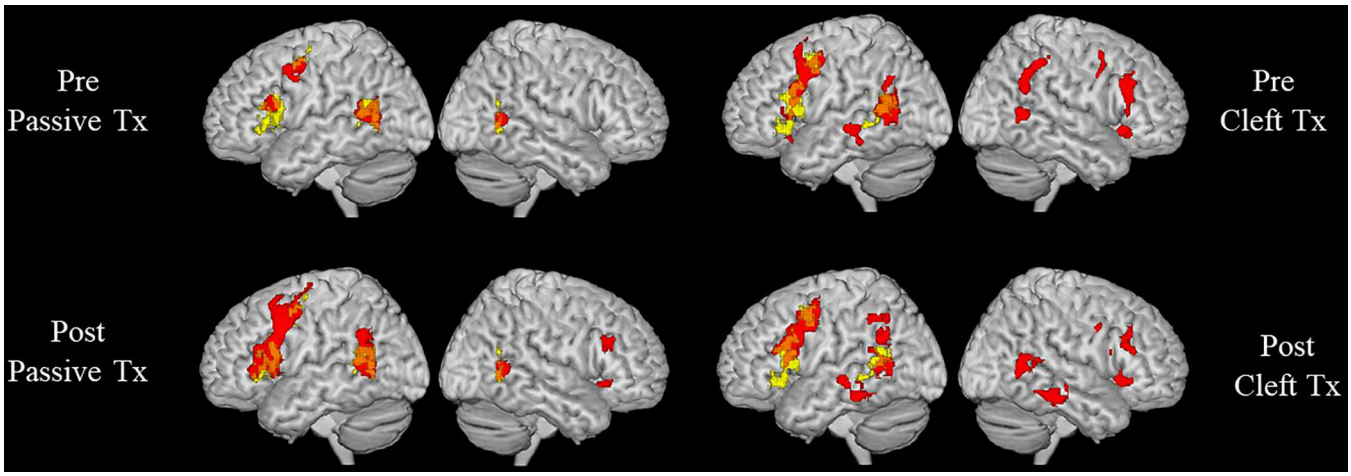

Figure 7.

ROI analysis results. Regions of BOLD signal activation prior to and following passive (contrast: passive>control) or object cleft (contrast: object cleft>control) treatment are displayed in red for DK and overlaid onto healthy controls' activation patterns for the same contrasts (yellow). The Figure reflects the results of voxel-wise analysis restricted to set of regions of interest (ROIs) that were selected (bilaterally) based on a recent meta-analysis of sentence processing studies (Walenski et al., 2019).

Table 1. A.

Published studies investigating the effects of behavioral treatment by language domain for patients with primary progressive aphasia (PPA) from 2010 to 2019 (PPA-G: 24; PPA-L: 9; PPA-S: 15; mixed PPA: 2).

Treatment Target	Number of Studies	# of participants with improved language	Author (year)
Naming	11	21/25	Beales et al. (2016) Beeson et al. (2011) Croot et al. (2015) Croot et al. (2019) Flanagan et al. (2016) Henry, Rising et al. (2013) Jafari et al. (2018) Macoir et al. (2015) Meyer et al. (2015) Meyer et al. (2016) Rebstock & Wallace (2018)
Narrative production	1	10/10	Henry, Hubbard et al. (2018)
Communication	2	11/11	Farrajota et al. (2012) Goral-Polrola et al. (2016)
Spelling	1	1/1	Tsapkini & Hillis (2013)
Word retrieval & grammar	1	2/2	Hameister et al. (2017)
Apraxia of speech	1	1/1	Henry, Meese et al. (2013)
Total	**17**	**46/50**	

Table 1. B.

Published studies examining the effects of noninvasive neural stimulation on language improvement across language domains in patients with primary progressive aphasia (PPA) from 2010 to 2018 (PPA-G: 44; PPA-L: 14; PPA-S: 22, unreported subtype: 1).

Treatment Target	Number of Studies	# of participants with improved language	Authors (year)
tDCS			
Naming	1	8/8 treated 8/8 placebo	Cotelli et al. (2014)
Language	2	7/7	Gervits et al. (2016) Wang et al. (2013)
Spelling	2	42/42	Tsapkini et al. (2014) Tsapkini et al. (2018)
rTMS			
Naming	1	10/10 nfvPPA 0/4 svPPA	Cotelli et al. (2012)
Cognitive function	1	1/1 participant (language only)	Trebbastoni et al. (2012)
Verb and noun inflection	1	1/1 PPA (verbs only)	Finocchiaro et al. (2006)
Total	**9**	**77/81**	

Table 2.

DK's performance on language measures across phases of the study.

Language Measure	Pre-Passive Treatment	Post-Passive Treatment	6-Months Post-Passive Treatment	12-Months Post-Passive/ Pre-Object Cleft Treatment	Post-Object Cleft Treatment	6-Months Post-Object Cleft Treatment	Healthy Adults' Performance*
Northwestern Naming Battery							
Noun Comprehension	100%	96.70%	100%	NA	90%	97%	
Verb Comprehension	100%	100%	100%	NA	100%	100%	
Noun Naming	82%	90%	94%	NA	70%	66%	
Verb Naming	100%	81%	88%	NA	75%	81%	
Pyramids and Palm Trees	98%	100%	98%	NA	NA	100%	
Northwestern Assessment of Verbs and Sentences							
Verb Comprehension Test (Total)	100%	100%	100%	100%	100%	100%	
Verb Production Test (Total)	91%	95%	95%	72%	69%	86%	
Intransitive	100%	100%	100%	80%	80%	60%	
Transitive	90%	100%	100%	100%	70%	90%	
Ditransitive	86%	86%	86%	43%	57%	100%	
Argument Structure Production Test (Total)	72%	94%	91%	97%	57%	72%	
Intransitive	100%	100%	100%	100%	40%	100%	
Transitive	87%	100%	93%	100%	80%	80%	
Ditransitive	42%	83%	83%	92%	33%	50%	
Sentence Comprehension Test (Total)	90%	83%	97%	87%	80%	83%	
Canonical	100%	100%	100%	93%	80%	93%	
Noncanonical	80%	67%	93%	80%	80%	73%	
Sentence Production Test (Total)	40%	79%	73%	43%	33%	43%	
Canonical	40%	80%	87%	53%	47%	60%	
Noncanonical	40%	60%	60%	33%	20%	20%	
Northwestern Assessment of Verb Inflection							
Total Score	58%	63%	58%	58%	NA	43.33	
Nonfinite	85%	100%	80%	80%	NA	75%	
Finite	30%	50%	40%	40%	NA	13.33%	
Cinderella Narrative Analysis							

Language Measure	Pre-Passive Treatment	Post-Passive Treatment	6-Months Post-Passive Treatment	12-Months Post-Passive/ Pre-Object Cleft Treatment	Post-Object Cleft Treatment	6-Months Post-Object Cleft Treatment	Healthy Adults' Performance*
MLU (words)	5.67	6.46	7.55	7.42	5.25	5.89	11.11
WPM	53.755	51.468	47.4	45.876	36.129	40.9	132.22
Sentences with correct syntax	55%	73%	30%	38%	33.33%	39.29%	93.02%
Open:Closed class ratio	0.982	0.906	0.939	0.934	1.454	1.259	0.95
Noun:Verb ratio	1.381	0.983	1.79	1.423	1.407	1.457	1.21
Verbs with correct argument structure	76%	95%	93%	96%	92%	93.94%	98%
Correct grammatical morphology: verbs	71%	90%	88%	100%	96%	83.33%	99%

* Older adult performance from Thompson et al., 2012. MLU=mean length of utterance; WPM=words per minute.

Table 3.

Sentence types and examples used for training (1, 5), generalization testing to linguistically-related structures during passive (2, 3, 4) and object-cleft treatment (6), and linguistically-unrelated structures tested during passive training (5) and object-cleft training (1,7).

N	Sentence type	Example
1	Long Passives	*The boy was shaved by the man in the barbershop*
2	Short Passives	*The boy was shaved by the man (a)*
		The boy was shaved in the barbershop (b)
3	Actives with unaccusative verbs	*The woman was falling on the stairs*
4	Actives with transitive verbs	*The boy was shaving the man in the barbershop*
5	Object Cleft	*It was the boy who the man shaved*
6	Object Wh-question	*Who was the boy shaving?*
7	Pronominal Structure	*The man knew that the boy shaved him*

Table 4.

Results of the mixed-effects regression analyses run on production and comprehension scores. For each comparison, regression parameter estimates (i.e., betas), standard error (SE), statistics and p-values are provided.

			Production				Comprehension			
Phase	**Structure**	**Comparison**	**Estimate**	**SE**	**z-value**	**p-value**	**Estimate**	**SE**	**z-value**	**p-value**
Passive Training Phase	Long Passive (trained)	post vs. pre-treatment	2.398	0.870	2.755	0.006	0.348	0.839	0.415	*n.s.*
		6months vs. pre-treatment	3.145	1.120	2.808	0.005	0.811	0.932	0.87	*n.s.*
		1year vs. pre-treatment	1.587	0.717	2.212	0.027	1.558	1.168	1.334	*n.s.*
	Short Passive (untrained)	post vs. pre-treatment	2.248	0.575	3.908	<.0001	−0.636	0.812	0.784	*n.s.*
		6months vs. pre-treatment	2.499	0.616	4.055	<.0001	−0.348	0.839	−0.415	*n.s.*
		1year vs. pre-treatment	1.539	0.496	3.105	0.002	0.463	0.973	0.475	*n.s.*
	Active Unaccusative (untrained)	post vs. pre-treatment	0.000	0.000	0.000	*n.s.*				
		6months vs. pre-treatment	−0.405	0.904	−0.449	*n.s.*		**		
		1year vs. pre-treatment	0.847	0.936	0.905	*n.s.*				
	Active Transitive (untrained)	post vs. pre-treatment	1.025	0.654	1.566	*n.s.*	1.35	0.891	1.515	*n.s.*
		6months vs. pre-treatment	0.205	0.641	0.32	*n.s.*	2.097	1.136	1.846	0.065
		1year vs. pre-treatment	0.205	0.641	0.32	*n.s.*	0.251	0.71	0.354	*n.s.*
	Object Cleft (untrained)	post vs. pre-treatment					0.251	0.71	0.354	*n.s.*
		6months vs. pre-treatment		***			0.48	0.697	0.688	*n.s.*
		1year vs. pre-treatment					0.251	0.71	0.354	*n.s.*
OC Training Phase	Object Cleft (trained)	post vs. pre-treatment	3.145	1.12	2.808	0.005	1.048	0.663	1.58	*n.s.*
		6months vs. pre-treatment	2.539	1.212	2.095	0.036	2.234	0.929	2.404	0.016
	Object Wh-questions (untrained)	post vs. pre-treatment	1.792	0.874	2.05	0.04	−0.288	0.761	−0.378	*n.s.*
		6months vs. pre-treatment	−1.792	0.986	1.817	0.069	−0.981	0.854	−1.149	*n.s.*
	Pronominal (untrained)	post vs. pre-treatment					1.253	0.762	1.644	*n.s.*
		6months vs. pre-treatment		***			1.253	0.945	1.326	*n.s.*
	Long Passive (untrained)	post vs. pre-treatment	−0.767	0.723	−1.052	*n.s.*	0.054	1.452	0.037	*n.s.*
		6months vs. pre-treatment	−0.901	0.854	−1.149	*n.s.*	1.558	1.295	1.203	*n.s.*
	Active Unaccusative (untrained)	post vs. pre-treatment	1.253	0.945	1.326	*n.s.*		**		

** = model did not converge because accuracy was the same across time points.

*** = model did not converge, as accuracy was 0% across time points.

Table 5.

Performance on tests of cognitive function administered prior to passive and object cleft treatment.

		Pre-Passive Treatment			Pre-Object Cleft Treatment			Post-Object Cleft Treatment		
Cognitive Process	**Test**	**Score**	**%tile/z/ss**	**Class**	**Score**	**%tile/z/ss**	**Class**	**Score**	**%tile/z/ss**	**Class**
Visual-Spatial Working Memory	WMS-R-IV Spatial Addition	N/A	N/A	N/A	7/24	8 (ss)	Average	7/24	8 (ss)	Average
Visual Working Memory	WMS-R-IV Symbol Span	N/A	N/A	N/A	20/50	12 (ss)	High Average	19/50	10 (ss)	Average
Verbal Learning Memory	WMS-R Logical Memory (Part I)	15/50	21st %	Low Average	11/50	7th %	Mild	9/50	6th %	Mild
Visual Learning Memory	WMS-R Visual Rep (Part I)	35/41	98th %	Very Superior	30/41	76th %	High Average	32/41	88th %	High Average
Spatial Learning Memory	WMS-R-IV Designs (Part I)	N/A	N/A	N/A	62/120	10 (ss)	Average	58/120	9 (ss)	Average
Verbal Delayed Recall	WMS-R Logical Memory (Part II)	14/50	52nd %	Average	14/50	52nd %	Average	8/50	52nd %	Average
Visual Delayed Recall	WMS-R Visual Rep (Part II)	35/41	99th %	Very Superior	27/41	90th %	Superior	25/41	84th %	High Average
Spatial Delayed Recall	WMS-R-IV Designs (Part II)	N/A	N/A	N/A	56/120	12 (ss)	High Average	51/120	11 (ss)	Average
Attention	Target Cancellation Test	time: 84s errors: 2	---	---	time: 94s errors: 2	---	---	time: 118s errors: 0	---	---
	Trail Making Test (Part A)	time: 54s errors: 0	---	---	time: 54s errors: 0	---	---	time: 48s errors: 0	---	---
Executive Attention	Trail Making Test (Part B)	time: 112s errors: 0	---	---	time: 184s errors: 1	---	---	time: 158s errors: 0	---	---
Abstract Reasoning/ Conceptual Flexibility	Wisconsin Card Sorting Test (categories)	5	2.18 (z)	Very Superior	5	2.18 (z)	Very Superior	5	2.18 (z)	Very Superior
	Wisconsin Card Sorting Test (errors)	8	2.467 (z)	Very Superior	9	2.3 (z)	Very Superior	10	2.13 (z)	Very Superior
	Raven Progressive Matrices	29/36	90th %	Superior	33/36	>95th %	Superior	N/A	N/A	N/A

WMS-R=Weschler Memory Scale Revised; %=percentile; z=z-score; SS=standard score; Class=classification; N/A=not administered.

Table 6.

DK's accuracy on the eye-tracking tasks, and thematic prediction and integration scores derived from performance of sentence-picture matching tasks administer at pre- and post- passive and object cleft treatment. Significant differences between DK's data and the control group (Crawford-Howell t-test; significance levels:

	DK pre-tx	DK post-tx	Healthy Control Participants† Mean (SD)
Accuracy (%, Comprehension)			
Active	96	100	
Passive	96	100	
Subject-cleft	83	75	
Object-cleft	4	8	
Accuracy (%, Production)			
Active	7	46#	
Passive	54	71#	
Eye movements (Comprehension)			
Passive sentence processing			
Prediction (V region)	0.41	0.5	0.40 (0.10)
Integration (N2 region)	0.29*	0.33*	0.66 (0.10)
Integration (S End region)	0.82	0.75	0.90 (0.14)
Object cleft sentence processing			
Prediction (N1)	0.44	0.37	
Integration (V + S End)	0.18	0.15	

* p< .05), as well as between pre- and post-treatment (mixed-effect logistic regression; significance levels:

# p<.05) are indicated.

† Data from Mack and Thompson (2017).

Table 7.

Results of the nonparametric voxel-based morphometry (VBM) analysis comparing DK's gray matter maps at each time point to a control group (N=76). The Table shows significant clusters at a cluster-level threshold of p<.001, FWE-corrected (p<.05), with labels derived from Harvard-Oxford atlas (Desikan et al., 2006).

Pre- Passive Treatment								Post- Passive Treatment							
Cluster Size	Pseudo-t	Peak coordinates			Peak Region	Extent	L/R	Cluster Size	Pseudo-t	Peak coordinates			Peak Region	Extent	L/R
		x	y	z						x	y	z			
557	5.92	−30	2	−20	Amygdala	Hippocampus, Parahippocampal anterior	L	758	6.85	−29	0	−18	Amygdala	Hippocampus, Parahippocampal anterior, Insula, Temporal Pole	L
Pre- Cleft Treatment								**Post- Cleft Treatment**							
Cluster Size	Pseudo-t	Peak coordinates			Peak Region	Extent	L/R	Cluster Size	Pseudo-t	Peak coordinates			Peak Region	Extent	L/R
		x	y	z						x	y	z			
1899	6.85	−26	−10	−24	Hippocampus	Parahippocampal anterior, Temporal Pole, Caudate, Insula, Amygdala, Putamen, Accumbens, Planum Polare	L	1663	7.58	−26	−6	−21	Amygdala	Hippocampus, Parahippocampal anterior, Putamen, Accumbens, Insula, Temporal Pole, Temporal Fusiform anterior, Planum Polare	L
								240	5.63	−14	12	12	Caudate	Accumbens	L
								467	5.14	27	−4	−24	Amygdala	Hippocampus, Parahippocampal anterior, Temporal Pole	R

Table 8.

Significant clusters of activation found for *passive>control* and *object clefts>control* contrasts for heathy control participants (p<.001 uncorrected, cluster-level FWE<.05). Cluster size was determined by using AFNI's 3dClustsim, a permutating test function that simulates noise volumes to determine the cluster size corresponding to a given FWE threshold (i.e., p<.05), and corresponded to k>46 for *passive>control* and k>211 for *object clefts>control*.

Cluster size (k)	Peak T-value	Peak Coordinates			Peak Region	Extent	L/R
		x	y	z			
Passive>Control							
429	7.360	−40	−60	16	AG	MTG (temporo-occipital), SMG (posterior)	L
300	6.600	−58	16	4	IFG (pars opercularis)	IFG (pars triangularis)	L
201	6.090	−28	−8	50	PCG		L
155	8.170	46	−58	4	MTG (temporo-occipital)	AG	R
Object Cleft>Control							
739	7.140	−44	20	18	IFG (pars opercularis)	IFG (pars orbitalis), Insula	L
337	7.060	−40	6	48	MFG	PCG	L
433	6.730	−40	−60	18	AG	STG (posterior), MTG (posterior, temporo-occipital)	L

Note. Labels were derived from the Harvard-Oxford atlas (Desikan et al., 2006). AG = Angular Gyrus; IFG = Inferior Frontal Gyrus; MFG = Middle Frontal Gyrus; MTG = Middle Temporal Gyrus; PCG = Precentral Gyrus; SMG = Supramarginal Gyrus; STG = Superior Temporal Gyrus.

Table 9.

Regions of significant activation (pre-treatment, post-treatment) and upregulation of activation (post- minus pre-treatment) for DK, derived from the sentence verification tasks for the contrast *passive>control* (p<.001 uncorrected, cluster-level FWE<.05).

Passive>Control (Pre-Passive Treatment)							
Cluster Size	**Peak T-value**	**Peak Coordinates**			**Peak Region**	**Extent**	**L/R**
		x	**y**	**z**			
350	10.729	−38	2	46	MFG	PCG	L
414	8.322	−46	−60	8	MTG (temporo-occipital)	AG	L
136	5.724	−54	20	16	IFG (pars opercularis)	IFG (pars triangularis)	L
108	6.409	50	−54	8	MTG (temporo-occipital)		R
Passive>Control (Post-Passive Treatment)							
Cluster Size	**Peak T-value**	**Peak Coordinates**			**Peak Region**	**Extent**	**L/R**
		x	**y**	**z**			
1608	9.965	−38	0	48	MFG	IFG (pars opercularis, pars triangularis), PCG, Frontal Operculum	L
757	6.672	−54	−52	8	MTG (temporo-occipital)	AG, SMG (posterior)	L
174	6.332	48	−54	6	MTG (temporo-occipital)		R
101	4.240	40	30	−4	IFG (pars orbitalis)	Insula, Frontal Operculum	R
93	4.458	50	28	26	MFG	IFG (pars triangularis)	R

Note. Labels were derived from the Harvard-Oxford atlas (Desikan et al., 2006). AG = Angular Gyrus; IFG = Inferior Frontal Gyrus; MFG = Middle Frontal Gyrus; MTG = Middle Temporal Gyrus; PCG = Precentral Gyrus; SMG = Supramarginal Gyrus; STG = Superior Temporal Gyrus.

Table 10.

Regions of significant activation (pre-treatment, post-treatment) and upregulation of activation (post minus pre-treatment) for DK, derived from the sentence verification tasks for the contrast *object cleft>control* (p<.001 uncorrected, cluster-level FWE<.05).

Object Cleft>Control (Pre-Cleft Treatment)							
Cluster Size	Peak T-value	Peak Coordinates			Peak Region	Extent	L/R
		x	y	z			
997	11.234	−38	0	46	MFG	IFG (pars opercularis, pars triangularis), PCG	L
637	7.565	−58	−58	14	AG	SMG (posterior), MTG (temporo-occipital)	L
202	6.485	−68	−28	−4	MTG (posterior)	STG (posterior)	L
106	4.069	−28	24	−8	IFG (pars orbitalis)	Insula	L
347	8.670	50	26	28	MFG	IFG (pars triangularis)	R
237	5.813	56	−52	26	AG	SMG (posterior)	R
220	5.968	38	22	−8	IFG (pars orbitalis)	Insula, Frontal Operculum	R
141	5.396	40	6	38	MFG	PCG	R
121	6.649	48	−54	6	MTG (temporo-occipital)		R
Object Cleft>Control (Post-Cleft Treatment)							
Cluster Size	Peak T-value	Peak Coordinates			Peak Region	Extent	L/R
		x	y	z			
1348	11.889	−38	0	48	MFG	IFG (pars opercularis, pars triangularis), PCG	L
495	5.896	−48	−62	8	MTG (temporo-occipital)	AG	L
212	6.867	−60	−24	−2	STG (posterior)	MTG (posterior, temporo-occipital), ITG (posterior, temporo-occipital)	L
188	7.491	−38	−58	44	AG	SMG (posterior)	L
235	6.611	50	−60	2	MTG (temporo-occipital)	AG	R
229	6.711	38	24	−6	IFG (pars orbitalis)	Insula, Frontal Operculum	R
196	7.212	62	−38	−16	MTG (posterior)	ITG (posterior)	R
196	6.944	42	24	22	MFG	IFG (pars opercularis, pars triangularis)	R
151	7.143	38	2	36	PCG	IFG (pars opercularis), MFG	R

Note. Labels were derived from the Harvard-Oxford atlas (Desikan et al., 2006). AG = Angular Gyrus; IFG = Inferior Frontal Gyrus; MFG = Middle Frontal Gyrus; MTG = Middle Temporal Gyrus; PCG = Precentral Gyrus; SMG = Supramarginal Gyrus; STG = Superior Temporal Gyrus.