

Improved language performance subsequent to low-frequency rTMS in patients with chronic non-fluent aphasia post-stroke

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Background: Low-frequency repetitive transcranial magnetic stimulation (rTMS) has emerged as a potential tool for neurorehabilitation and remediation of language in chronic non-fluent aphasia post-stroke. Inhibitory (1 Hz) rTMS has been applied to homologous language sites to facilitate behavioural language changes. Improvements in picture-naming performance and speech output over time have been reported.

Methods: Low-frequency (1 Hz) rTMS was applied to six real stimulation and six sham placebo patients for 20 min per day, for 10 days, and behavioural language outcome measures were taken at baseline (pre-stimulation) and 2 months post-stimulation.

Results: The findings demonstrate treatment-related changes observed in the stimulation group when compared to the placebo control group at 2 months post-stimulation on naming performance as well as other aspects of expressive language and auditory comprehension.

Conclusions: These findings provide considerable evidence to support the theory of rTMS modulating mechanisms of transcallosal disinhibition in the aphasic brain and highlight the potential clinical applications for language rehabilitation post-stroke.

Introduction

Recent experimental trials of low-frequency repetitive transcranial magnetic stimulation (rTMS) applied to patients with chronic non-fluent aphasia have demonstrated its capacity to modulate and inhibit extraneous levels of right hemisphere (RH) activation in homologous language sites, which may impede language recovery in some patients [1]. Overactivation in RH frontal regions including the inferior frontal gyrus (IFG) and the motor cortex has previously been identified using functional neuroimaging in populations of persons with aphasia post-stroke. [1–4].

There is now considerable evidence to suggest that rTMS to the apical portion of Broca's area homologue, pars triangularis (dorsal and posterior), can result in improved language function for patients with non-fluent aphasia. [5,6]. For example, improvements in behavioural language performance following 10 days of

low-frequency rTMS (1 Hz, inhibitory) has been demonstrated in a small group of patients with non-fluent aphasia [5]. Language improvements to date are reported primarily for functions related to picture naming in case studies and small patient samples (e.g. four patients) at 8 months post-stimulation and up to 43 months post-stimulation [2,5,7–9]. Hamilton *et al.* [6] suggest that the application of rTMS to the intact contralateral hemisphere may induce effects that generalize beyond naming to propositional speech including spontaneously elicited speech using picture stimuli.

With reference to the theory of transcallosal disinhibition proposed by Heiss and Theil [10], rTMS has been applied to a language homologue in the RH to inhibit extraneous activity identified on previous functional neuroimaging studies in patients with non-fluent aphasia in the IFG [11,12] and in patients with left hemisphere (LH) brain tumours [13]. High levels of activation found in homologous language centres post-stroke suggest an interhemispheric shift in neural language networks to recruit undamaged neural resources in the unaffected hemisphere [14,15]. Recruitment of RH sites post-stroke represented by increased cortical activation is postulated to be less efficient in language

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recovery than LH regions [10]. It is possible that mechanisms of transcallosal disinhibition may facilitate downregulation of overactive homologous language sites and upregulation of LH language networks, yielding functional language improvements over time. The theory of mutual inhibition of LH language sites in the lesioned brain has provided the framework for previous investigations into the effects of rTMS in chronic aphasia [2,5,6,9,16].

The present study aimed to elucidate the effects of rTMS on the aphasic brain at 2 months post-stimulation, with respect to behavioural language measures and to address some of the inadequacies of existing research in this field by improving on sample size numbers, utilizing state of the art neuronavigational techniques and including a placebo control group as a comparative measure of treatment group language changes over time with double-blinded assessments. This research aims to test current hypotheses regarding the ability of low-frequency rTMS to inhibit overactivation in the homologue to Broca's area and induce behavioural language improvements in picture-naming function over time. It is proposed that the suppression of the right pars triangularis using rTMS will modulate prefrontal and temporo-parietal neural connections responsible for naming processes to facilitate behavioural improvements in naming performance and propositional speech.

Materials and methods

Patients

Twelve (12) right-handed patients with chronic aphasia received rTMS. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). All patients had suffered a left middle cerebral artery (MCA) stroke between 2–6 years previously and had residual language impairments. A double-blind methodology was employed where patients were *randomly* assigned to one of two groups either receiving *real condition* TMS [$n = 6$, aged between 54 and 67 years; mean age (SD) = 60.8 (5.98) years; mean time post-stroke (SD) = 3.49 (1.27) years] or a *placebo* TMS (using a SHAM coil) [$n = 6$, aged between 51 and 85 years; mean age (SD) = 67 (13.11) years, mean time post-stroke (SD) = 3.46 (1.53) years]. Table 1 provides detailed biographical information about the patients who participated in the present study.

Patient recruitment and screening

Patients were recruited through two major metropolitan hospitals and university research databases in the

Greater Brisbane region, Australia. Ethical clearance was granted from the Royal Brisbane and Women's Hospital, Princess Alexandra Hospital and the University of Queensland ethical review boards. All patients gave informed consent to participate in this research, and procedures conformed with the declaration of Helsinki. Patient exclusion criteria for rTMS were derived from guidelines published by Wasserman [17]. Participants did not receive speech therapy services during their participation in this research study.

Neuroimaging and cortical target identification

Prior to stimulation, all subjects were required to undertake a 3-Tesla structural magnetic resonance imaging (MRI) scan to aid target localization and to provide additional information on the size, extent and composition of the lesion. Figure 1 shows examples of MRIs from two of the stimulated patients. Acquisition parameters were as follows: TR = 19 msec, TE = 4.92 msec, matrix size = 256×256 , number of slices = 128, slice thickness = 2 mm. The study neuroradiologist provided a radiological report to specify affected neural regions. A computerized MRI visualization and analysis system [18] was then employed to visually mark target areas [homologue to Brodmann area 45 (BA 45) and the right motor hand knob] with a crosshair (i.e. +).

The language-related cortical area in the contralateral (right) hemisphere (i.e., homologue to BA 45) was established as the stimulation target. The foot of the third frontal convolution represents the classical definition of Broca's area [19]. Within the left IFG, this region incorporates the structures pars triangularis and pars opercularis, also known as BA 45 and BA 44, respectively. The cytoarchitecture of Broca's area was informed by papers from Amunts *et al.* [20,21]. Previous studies have revealed TMS of BA 45 (pars triangularis) and not BA 44 (pars opercularis) significantly increases the accuracy and decreases reaction time of picture naming in patients with aphasia [5,8]. The apical portion of right BA 45 was therefore selected as the specific stimulation point for the present study, delimited ventrally by the horizontal ramus of the Sylvian fissure [22] and laterally by the vertical ramus of Sylvian fissure. Figure 2 shows the stimulation target marked on 3D reconstruction of the patient's brain.

Neuronavigational techniques

Once the target was marked on the image, the MRIs were imported into the *Stealthstation Treon* (Medtronic, Minneapolis, MN, USA), a frameless stereotactic image

Table 1 Patient biographical information

Patient	Sex	Age	Edinburgh Handedness Inventory score	Handedness	Years of education	Lesion site	Time post-stroke to initial testing (years; months)	Hemiparesis	Aphasia diagnosis	Stimulation group
rTMS 1	F	65	80	R	18	Long-standing left middle cerebral artery (L MCA) territory infarct with ex-vacuo dilatation of the left lateral ventricle.	4; 5	No	Mild–moderate non-fluent	Real
rTMS 3	M	59	50	R	12	L MCA infarct with ex-vacuo dilatation of the left lateral ventricle and encephalomalacia in the left insula and left parieto-occipital region.	3; 3	No	Moderate-severe non-fluent/global	Real
rTMS 4	F	66	100	R	14	L MCA infarct with encephalomalacia and ex-vacuo dilatation of the left lateral ventricle. The sylvian fissure is enlarged. The encephalomalacia extends superiorly and medially to involve the medial aspect of the left motor strip.	5; 8	Yes	Moderate non-fluent	Real
rTMS 9	M	67	100	R	16	Significant L MCA territory infarct with encephalomalacia and ex-vacuo dilatation of the left lateral ventricle. The Basal nuclei are largely spared.	2; 6	No	Severe non-fluent/global	Real
rTMS 10	M	54	60	R	10	Mature L MCA infarct extending laterally from the posterior horn of the left lateral ventricle with encephalomalacia and ex-vacuo dilatation of the ventricle. Small lacunar type infarcts bilaterally. Normal posterior fossa structures.	3; 5	Yes	Severe non-fluent/global	Real
rTMS 13	M	54	100	R	10	L MCA territory infarct with a significant area of encephalomalacia in the left frontal lobe and associated ex-vacuo dilatation of the left ventricle and left cerebral peduncle reduction.	2; 5	Yes	Mild-moderate non-fluent	Real

guidance system designed for neurosurgical application but adapted for this research via several custom software modifications. Figure 3 shows the setup of the neuronavigational system. Within the Stealthstation, the ‘hot spot’ was converted to a target plan. Reflective

markers attached to the subject’s head were detected via an infrared tracking camera, subsequently logging the position of the head in space. The software then co-registered the position of the subject’s head with the MRI data set.

Table 1 (Continued)

Patient	Sex	Age	Edinburgh Handedness Inventory score	Handedness	Years of education	Lesion description	Time post-stroke to initial testing (years; months)	Hemiparesis	Aphasia diagnosis	Stimulation group
rTMS 2	M	72	100	R	14	L inferior division MCA infarct with an accompanying temporo-parietal encephalomalacia.	4; 0	No	Mild-moderate non-fluent	Sham
rTMS 5	F	51	100	R	13	L CVA, total anterior circulation infarct with an extensive left hemisphere MCA/stroke with gross encephalomalacia. There is a hyperintense collection over the left hemisphere which is assumed to represent a subacute subdural haematoma. The right hemisphere appears normal. There is atrophy of the left cerebral peduncle and left side of the pons, in keeping with Wallerian degeneration.	3; 4	Yes	Moderate non-fluent	Sham
rTMS 8	M	77	100	R	13	L MCA territory infarct with subacute right occipital (posterior cerebral artery) territory infarct. A couple of small globular foci are seen in the deep white matter of both cerebral hemispheres consistent with chronic ischaemia related to microvascular disease.	2; 2	No	Mild-Moderate non-fluent	Sham
rTMS 11	M	66	80	R	12	L MCA territory infarct with encephalomalacia involving the left frontal lobe and moderate ex-vacuo dilatation of the left lateral ventricle. The right hemisphere and the posterior fossa structures appear relatively normal (Wallerian degeneration noted left upper brain stem)	2; 3	Yes	Moderate non-fluent	Sham
rTMS 14	M	71	100	R	10	Significant L MCA territory infarct with moderate ex-vacuo dilatation of the left ventricle and temporo-parietal encephalomalacia	2; 9	Yes	Moderate-severe non-fluent	Sham
rTMS 15	M	63	100	R	15	Large L MCA territory infarct with significant tissue loss with ex-vacuo dilatation of the left ventricle. The right hemisphere and posterior fossa structures appear normal	6;3	Yes	Severe non-fluent/global	Sham

rTMS, repetitive transcranial magnetic stimulation.

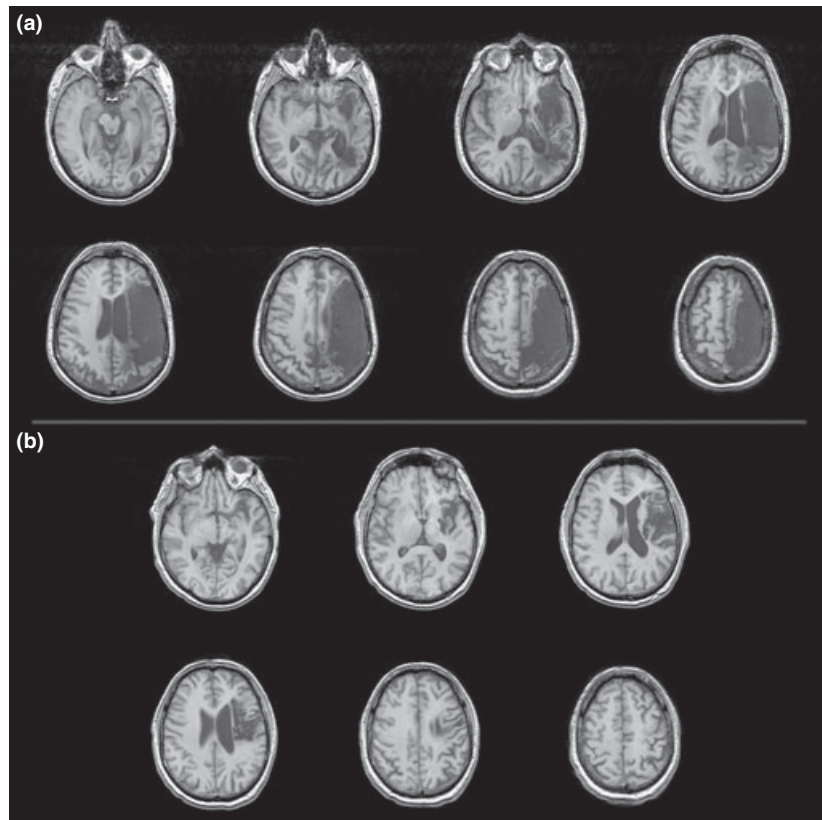


Figure 1 Structural 3T magnetic resonance imaging scans for two patients of the twelve patient cohort, demonstrating the range of lesion severities (a) Participant rTMS 15 (b) Participant rTMS 13.

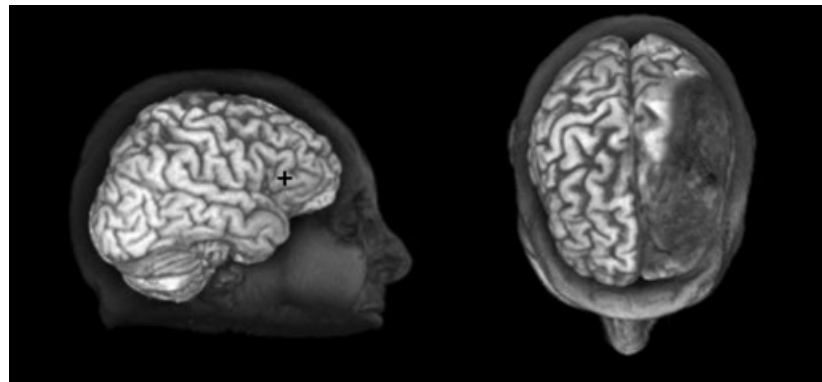


Figure 2 A 3D brain surface reconstruction from 3T structural magnetic resonance imaging scan of participant rTMS 5. The target is defined as the apical portion of Brodmann area 45 homologue, delimited ventrally by the horizontal ramus of the sylvian fissure and laterally by the vertical ramus of sylvian fissure.

Resting Motor Threshold (rMT)

The TMS coil (bi-phasic stimulation) was placed on the motor 'hot spot' for the first dorsal interosseous (FDI) muscle in the left hand (i.e. knob within pre-central gyrus) in the contralateral hemisphere as determined by MRI marking and Stealthstation software (Medtronic, USA). Motor-evoked potentials (MEPs) were then elicited via TMS and surface EMG recorded from FDI via Ag/AgCl electrodes (1 cm in diameter), positioned over the belly of the muscle and the metacarpo-phalangeal joint of the index finger, respectively. rMT was

defined as the minimum stimulus intensity eliciting five responses of about 50 μ V of 10 consecutive trials (50% successful MEPs) in the relaxed contralateral FDI [23]. For the present research study on stroke patients, stimulation was applied at 90% of the rMT attained [5,8,16]. Patient stimulation intensities ranged between 35–55% of maximum stimulator output.

Stimulation protocol

Low frequency, 1 Hz rTMS was applied to patients for 20 min per day (1200 pulses), for 10 days (10 sessions)



Figure 3 Diagram showing setup of repetitive transcranial magnetic stimulation equipment and stereotactic neuro-navigation system, Stealthstation Treon (Medtronic, Minneapolis, USA). Reflective markers on the coil and patient's head facilitate the Stealthstation's infrared camera to guide the positioning of the coil over the marked target on the anterior portion of Brodmann area 45 (pars triangularis) over the 10-day testing block.

as defined by Naeser *et al.* [5] The stimulation protocol aimed to downregulating RH overactivation in homologous language sites. The TMS target was the anterior portion of homologue to right pars triangularis (BA 45) in Broca's area as cited in previous rTMS studies as that location consistently results in the best response to rTMS [2,5,16]. A figure of eight, 70 mm diameter rTMS coil and identical sham coil were utilized (Magstim, Carmarthenshire, Wales, UK).

Sham stimulation

The sham stimulation group in this study served as a placebo control condition. The sham coil employed (Magstim, Carmarthenshire, Wales, UK) was identical in shape and size to the real stimulation coil and produced the same audible click as the real coil without the production of a magnetic field. As the sham TMS coil does not activate the cortex, stimulation in this condition would not induce neuro-physiological changes that could influence behavioural language function. Sham stimulation was used to verify the effects of the real stimulation protocol as a comparative control measure.

Language outcome measures

Standardized language assessments, administered by a speech-language pathologist who was blinded as to

whether the participant had received real TMS stimulation or sham stimulation, were utilized to measure changes in behavioural language function associated with rTMS treatment. One week prior to stimulation (baseline) and 2 months post-stimulation, patients were tested using the standard form of the Boston Naming Test (BNT) [24] and selected subtests of the Boston Diagnostic Aphasia Examination (BDAE) [25]. Subtests were administered according to a protocol outlined by Naeser *et al.* [5]. Receptive and expressive language abilities were tested. The subtests administered were the following: picture description (Cookie Theft Picture) (analysis of complexity index and longest number of words per phrase length), word comprehension, word comprehension by category, commands, complex ideational materials, repetition (single words, non-words and sentences), responsive naming, naming screening of special categories, naming colours, naming actions, naming animals, naming tools and implements.

Additionally, a set of 144 black and white line drawings of objects, taken from a previously published common object picture inventory [26], was used to measure changes in picture naming. Pictures were administered in lists of 48 words, balanced for average response latency, syllable length, frequency and visual complexity and percentage agreement. Norms pertaining to these variables were obtained from the online International Picture Naming Database. Verbal

responses were recorded via a microphone positioned approximately 10 cm from the subject's mouth.

A series of two-way repeated measures analyses of variance (ANOVA) were conducted for all BDAE subsets including the BNT, picture-naming accuracy and latency, by time of testing (two levels, baseline, prior to TMS vs. 2 months post-TMS) and group (real stimulation vs. sham). *Post hoc* analyses were conducted between the two groups using an independent samples *t*-test at baseline and 2 months post-rTMS. A repeated measures *t*-test was used to measure within-group performance, baseline to 2 months.

Results

The individual patient assessment results on the comprehensive language battery are presented in Appendixes S1–S4. Appendix S5 outlines mean values, standard deviations, significant interactions and effect size. Significant interactions of group (rTMS, sham) \times time (baseline, 2 months) were identified for the following subtests: BDAE naming actions ($P < 0.01$), BDAE naming tools and instruments ($P < 0.05$), BDAE repetition of sentences ($P < 0.05$), Cookie Theft picture description complexity index ($P < 0.05$), Cookie Theft picture description longest words per phrase ($P < 0.01$), Commands ($P < 0.05$), the overall score calculated from the BDAE subtests administered ($P < 0.01$), The BNT ($P < 0.05$), Snodgrass and Vanderwart [26] picture-naming latency ($P < 0.05$) and Snodgrass and Vanderwart [26] picture-naming accuracy ($P < 0.05$).

Post hoc analyses

Post hoc analyses revealed no significant differences between the real stimulation and sham conditions at baseline for all language subtests, ($P > 0.05$).

At 2 months post-stimulation, significant differences between the stimulation and sham group were found for a number of language subtests. The real stimulation group scored significantly higher on BDAE naming actions ($t = 4.16$, $P < 0.01$, $df = 10$), BDAE naming tools and instruments ($t = 3.00$, $P < 0.05$, $df = 10$), Cookie Theft picture description complexity index ($t = 4.05$, $P < 0.05$, $df = 10$), BDAE overall score ($t = 3.7$, $P < 0.05$, $df = 10$) and picture-naming accuracy [26] ($t = 3.21$, $P < 0.05$, $df = 10$). The real stimulation group performed significantly lower on the Snodgrass and Vanderwart [26] picture-naming latency ($t = 3.6$, $P < 0.05$, $df = 10$).

Within the real stimulation group, significant differences across time (baseline to 2 months post-stimulation) were found. Performance at 2 months

post-stimulation was higher on BDAE naming actions ($t = 2.609$, $P < 0.05$, $df = 5$), BDAE naming of tools and instruments ($t = 3.796$, $P < 0.01$, $df = 5$), BDAE overall score ($t = 4.145$, $P < 0.01$, $df = 5$), Commands ($t = 3.371$, $P < 0.05$, $df = 5$) and picture-naming accuracy [26] ($t = 3.162$, $P < 0.05$, $df = 5$). Performance at 2 months post-stimulation was significantly lower for picture-naming latency [26] ($t = 3$, $P < 0.05$, $df = 5$). No significant results within the sham group across time were found. As can be seen in Table 1, the age variance for the sham group was higher than for the participants receiving real stimulation. However, further statistical analysis failed to determine a significant age \times time interaction in the sham group for any language subtest ($P > 0.05$).

Discussion

The present research investigated the neuromodulatory effects of low-frequency inhibitory rTMS on a sample of twelve patients with non-fluent aphasia, including a sham (control) group to inform the behavioural language effects at 2 months post-stimulation. It was hypothesized that the effect of rTMS applied to language homologues in a left IFG-lesioned brain may be attributable to the downregulation of over activity in the homologue to Broca's area in patients with chronic aphasia. Comparisons between the real stimulation and sham conditions indicated significant interactions of group (rTMS, sham) \times time (baseline, 2 months) as well as within sample improvements observed for the real stimulation group. Significantly improved performance on the picture-naming subtests on the BDAE [25] and naming accuracy and latency on a standardized picture inventory [26] were found. In accordance with previous investigations linking lesions in the prefrontal cortex to deficits in action naming improvements [27,28], improved performance in action naming was observed 2 months post-stimulation for the real stimulation condition. The present results remain consistent with previous investigations in which picture naming notably improved, 8 months post-stimulation [5] on a cohort of four patients and case study reports up to 43 months post-stimulation [2]. Improvements in sentence complexity measured on the picture description subtest were also identified in the real stimulation group providing evidence that the effects of rTMS may extend beyond picture-naming performance to other aspects of language production. Comparable effects were reported by Hamilton *et al.* [6] in a recent single case report providing merit to arguments of further generalized language effects e.g. grammatical complexity and spontaneous speech, in response to rTMS. Although these investigations are considered preliminary, they

provide valuable evidence to show that rTMS effects in the aphasic brain may be wider reaching within the bilateral language system than first proposed.

Although the majority of rTMS studies present improved expressive language abilities, the present study reports significant differences and improvements in receptive language performance on an auditory commands subtest at 2 months post-stroke when compared to baseline measures. A study by Naeser *et al.* [9] treated a single patient using a protocol of continuous positive airway pressure (CPAP) combined with rTMS-documented significant improvements in auditory commands; however, it is unclear whether these are as a result of rTMS or increased oxygenation facilitated by CPAP. Additionally, Martin *et al.* [2] reported improvements in auditory comprehension on commands and complex ideational materials in a poor responding speech output patient to 6 months post-rTMS. Whilst the effects of rTMS on expressive language appear to be more concrete, the effects on receptive language remain inconclusive and require further investigation.

The present outcomes are in agreement with the theories of mutual inhibition of LH language sites in chronic non-fluent aphasia and the induction of plastic neural changes when rTMS is applied to RH homologous sites. Indeed, heterogeneity within the present aphasic sample may be a confounding factor when interpreting the significant differences identified in behavioural language between real stimulation and sham groups. Differences between the groups and within the groups in variables such as age, time post-stroke, lesion size and affected neural regions must all be taken into consideration. It is hypothesized that age and lesional variations may provide the greatest influence on rTMS responses within both groups.

Conclusion

This research provides favourable indication that rTMS can be applied to the unaffected RH in persons with aphasia to facilitate brain reorganization in accordance with the theories of transcallosal disinhibition. The results demonstrate significant treatment effects on behavioural language outcome measures of picture naming, spontaneous speech and auditory comprehension between the real stimulation and placebo control groups. With the emerging evidence regarding the positive effects on aspects of auditory comprehension and other aspects of linguistic output, supplementary investigations would be highly beneficial. Further longitudinal investigations are crucial to expand the evidence base and forge a path for rTMS as a clinical tool for the remediation of language deficits in aphasia.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Receptive language subtests.

Appendix S2. Repetition and picture description.

Appendix S3. Naming subtests.

Appendix S4. Snodgrass and Vanderwart Picture naming.

Appendix S5. Results of statistical analyses.

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