Nonverbal Semantic Decisions in Severe Aphasia: An fMRI Investigation with Test/Retest Reliability

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BACKGROUND

- Neural mechanisms underlying language recovery in aphasia are not well understood - those underlying recovery in severe aphasia, even less so.
- Recent neuroimaging investigations have debated lateralization of functional recovery:
  - Evidence for a significant role of right hemisphere (RH) includes Cappa et al. (1997); Thulborn et al. (1999); Gold & Kertesz (2000), especially implicating regions homotopic to damaged left hemisphere regions within the language network.
    - Nonetheless, questions remain as to the necessity and sufficiency of RH activation (Belin et al., 1996; Rosen et al., 2000; Naeser et al., 2002; 2004) to language recovery.
  - Evidence for ***more efficient recovery*** in patients with activation in undamaged LH perilesional regions includes Heiss et al. (1997; 1999); Karbe et al. (1998); Thiel et al. (1998); Perani et al. (2003).
  - Two recent studies measured brain activity in aphasia patients pre- and post- speech therapy intervention for naming (Leger et al., 2002; Cornelissen et al., 2003). Both observed increased LH perilesional activity, espec. L inf. parietal lobe, post-treatment.
- Few of these studies have included patients with severe aphasia, who are typically viewed as having a poor prognosis for language recovery.
- Although test-retest reliability is routinely demonstrated during collection of language data in single subject aphasia research, to our knowledge, this has not been demonstrated in fMRI studies investigating the underlying neural mechanisms in aphasia recovery.

PURPOSE AND HYPOTHESES

This study addressed the issue of test/retest fMRI reliability in two individuals with chronic, moderate-severe nonfluent aphasia, who had been trained with an alternative, icon-based computer "language" (Computer-assisted Visual Communication, C-ViC). During fMRI, they performed a button-box, yes/no semantic judgment task on C-ViC icon "sentences". We investigated the critical issue of intra-subject reliability by exploring similarities and differences in regions of activation during participants' performance of identical tasks twice on the same day. We also explored hemispheric lateralization and localization associated with different degrees of aphasia recovery in these two patients.

We hypothesized the following:

- Patients with severe aphasia can provide reliable fMRI data during language tasks.
- During fMRI, severe aphasia patients will activate RH regions homologous to LH areas previously associated with lexical-semantic functions, e.g., middle and inferior temporal gyri, fusiform gyrus and angular gyrus; and prefrontal areas. These patients may also activate undamaged LH regions as well as perilesional regions.
- Patients with "best response" to C-ViC training (Naeser, Baker et al., 1998) will demonstrate better performance (accuracy & RTs), and have different fMRI activation than those with "moderate response", e.g., greater LH activity in the "best" patients.

MATERIALS AND METHODS

Participants: 2 participants with chronic, moderate-severe nonfluent aphasia. Both were R-handed M, with LMCA stroke. Both had extensive, deep white matter lesion adjacent to ventricle, compatible with no meaningful speech (Naeser et al., 1989). See region 1 (medial subcallosal fasciculus - M Sc F) & region 2 (middle 1/3 periventricular white matter - M 1/3 PVWM) marked w/arrows (Figures 1 and 2).

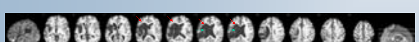


Figure 1. Structural MRI scan for Participant #1: 69 Yr. M, 11 Yr. poststroke onset; extensive subcortical lesion centered over the putamen w/ white matter lesion extension into M Sc F (red arrow)& M 1/3 PVWM (blue arrow); no lesion in Broca's or Wernicke's cortical areas; some cortical lesion present in the supramarginal gyrus and angular gyrus areas.

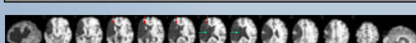


Figure 2. 59 Yr. M, 10 Yr. poststroke onset; extensive L MCA lesion; extensive cortical and subcortical lesion [some sparing in M Sc F (red arrow); however, extensive lesion in M 1/3 PVWM (blue arrow)]; cortical lesion also present in Broca's area, frontal operculum, sensorimotor mouth region, anterior supramarginal gyrus, Wernicke's area, and some ant. and post. MTG; also deep to the angular gyrus.

Both participants were classified with chronic, nonfluent aphasia as demonstrated by stable longitudinal testing scores on the Boston Diagnostic Aphasia Exam (BDAE; Goodglass & Kaplan, 1981) (See Table 1).

MATERIALS AND METHODS (cont'd.)

Table 1. Boston Diagnostic Aphasia Exam Subtest Scores for Participants

Patient Data			Auditory Comprehension				Repetition			Naming
Patient	MPO When Tested	Date When Tested	Auditory Compr'n: (Mean of 3 Percentiles)	Word Discrim'n	Commands	Complex Ideational Material	Single Word Rep'tn	High Prob	Low Prob	Visual Confrontation Naming
	Maximum Score:			72	15	12	10			114
1/ severe nonfluent	4.5 yr.	4/97 [a]	72.3	66	14	6	-	-	-	-
	6.5 yr.	2/99 [b]	69.3	68	11	7	1	-	-	8
2/ moderate nonfluent	10 mo.	7/94 [c]	38.3	46	9	3	8	1	0	28
	4 yr.	3/97	62.1	62.5	8	9	8	1	0	59
	10 yr.	5/03 [d]	74.3	65	13	9	9	-	-	12/20

[a] 2 yr. Post-C-ViC training; [b] 4.5 yr. Before fMRI; [c] immediately pre-C-ViC training; [d] 6 mo. Before fMRI

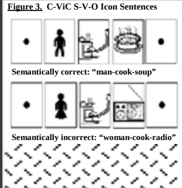
Experimental fMRI Design: During block design fMRI, participants were shown simple C-ViC "icon sentences" consisting of S-V-O, (i.e., subject-verb-direct object). Half contained a correct or appropriate direct object, e.g., "man cook soup" and half, an inappropriate (semantically unrelated) direct object, e.g., "woman cook radio".

Participants were asked to press a "yes" (left) button on a button box for semantically correct, and "no" (right) button for semantically incorrect sentences. Control condition consisted of passive viewing of checkerboard patterns (Figure 3, below). Participants judged 8 icon sentences per 2.5 minute run. Each icon sentence lasted for 7.5 seconds. Each session (TEST and RETEST) contained two identical runs, for a total of 16 icon sentences per session.

C-ViC Training: Participants were trained with a nonverbal, icon-based program, Computer-assisted Visual Communication (C-ViC) by 2nd author (EB). C-ViC is designed for individuals with severe aphasia and limited expressive output in oral, gestural, or written modalities. Patients also may have some impairment in auditory comprehension, ranging from moderate to severe impairment, and deficits in syntactic performance. In spite of these severe deficits, it has been demonstrated that some individuals with severe aphasia can learn to utilize this iconic system to express a range of communicative needs (Steele et al., 1989).

Participant #1 (59 Yr. M; 9 Mo. poststroke at entry into C-ViC; 11 Yr. at fMRI) had "moderate response" to training, and was unable to initiate communication with C-ViC. Participant #2 (49 Yr. M; 10 Mo. poststroke at C-ViC; 10 Yr. at fMRI) had "best response" to C-ViC training; he could use the icons to initiate communication on the computer (Naeser, Baker, et al., 1998).

Figure 3. C-ViC S-V-O Icon Sentences



Data Acquisition: Images (fMRI BOLD) were acquired using a 1.5T GE Signa scanner. Scout images were acquired in the sagittal plane. T1-weighted axial images parallel to the anterior commissure-posterior commissure (AC-PC) line. Whole head axial slices were acquired in 30 contiguous 5mm slices, FOV 24x24. Functional images were acquired in the same plane using echo-planar imaging (EPI), TR=3s, FOV=24x24, 64x64 matrix and an in-plane resolution of 3.12mm. A high-resolution 3D SPGR anatomical scan was also acquired. During each of two, 2.5 minute fMRI runs, each condition lasted 30 sec (4 stimuli at 7.5 sec. each), during which 10 scans were acquired. The resting (pattern) condition alternated with the yes/no button box task condition, for a total of 50 volumes (30 pattern; 20 task) with a total of 8 task stimuli per run. TEST session consisted of 2 runs separated by a 2-min. rest break. After completing four other, different C-ViC tasks in the scanner, RE-TEST (same 2 runs) was repeated.

Data Analysis: Data were analyzed with MatLab 6.5 (MathWorks, Natick, MA) and SPM2 (Wellcome Department of Cognitive Neurology, London, UK) on a Dell Workstation Precision 360. Images were realigned using the first image as a reference. Functional images were normalized to the MNI EPI image template with the resulting parameters applied to the T1-weighted anatomical image. Functional data were smoothed with a 6mm FWHM isotropic Gaussian kernel. The hemodynamic response was estimated and subsequent T-tests were performed [uncorrected p<.001; corrected Family Wise Error (FWE) p<.05] to determine task-related functional activation patterns. Significantly activated voxels were transformed from MNI space to the standard stereotaxic space of Talairach and Tournoux (1988) using MEDx 3.42 medical imaging processing software.

RESULTS

NOTE: The abstract reported a different Participant #2 (P #2). Subsequent analysis of her functional imaging revealed excessive motion artifact correlated with the task. Her data was dropped from this study.

Behavioral Results: (See Figure 4.)

P #1: Correctly judged 5/8 (run 1) and 7/8 (run 2) "sentences" on TEST and again 5/8 (run 1) and 7/8 (run 2) on RETEST to be appropriate or not. His errors were not the same between TEST and RETEST. Most consisted of accepting semantically unrelated icons, e.g., he judged "man build cheese" to be semantically acceptable. Mean RT (correct responses) was 2146 msec (SD=532 msec) on TEST and 1739 msec (SD=582 msec) on RETEST.

P #2: Correctly judged 7/7 (run 1) and 5/7 (run 2) on TEST and 8/8 (run 1) and 5/7 (run 2) on RETEST. Run 1 (TEST) contained too much motion artifact to analyze. In run 2, errors were the same between TEST and RETEST. One trial in both second runs was not registered by PsyScope, either due to a slow (or no) response. Mean RT (correct) was 3673 msec (SD =957 msec) on TEST and 2194 msec (SD=542) on RETEST.

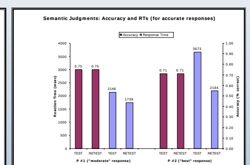


Figure 4. Accuracy and RTs during Test and Retest

Paired t-tests between participants' RTs demonstrated no significant difference between participants' RTs. Paired t-tests within participants' test and retest scores revealed both subjects were faster on retest (P #1: marginally significant, t=2.08, df=11, p=.062, mean difference=407 msec; P #2: t=3.68, df=4, p=.021, mean difference=1480 msec).

fMRI Results:

In general, strongly activated ROIs during TEST were also activated during RETEST, but less so (Table 2 and Fig.'s 5, 7).

P #1 ("moderate response" to C-ViC), whose subcortical lesion spares both Broca's and Wernicke's areas, failed to activate either of these LH regions. He only weakly activated R BA 44, and did not activate other RH homologous perisylvian regions (e.g., BA 22, 21, 45). See Table 2 and Figure 5. Some TEST/RETEST clusters of activation centered on identical local maxima, e.g., in the R medFG (BA 6). See Figure 6.

RESULTS (cont'd.)

fMRI Results (cont'd.):

P#2 ("best response" to C-ViC), also predominantly activated a network of right-lateralized language homologues, including R IFG (BA 45; 47) and R angular gyrus (BA 39). See Table 2 and Figure 5, below. He activated part of the L post. supramarginal gyrus (BA 40), a LH perilesional area. R IFG (BA 47) demonstrates response decrements typical of modulation by practice (Blasi et al., 2002). See Figure 7.

Table 2. Some Activation Foci in Predicted ROIs: Semantic Decisions vs. Rest [1]

Area [2]	Case 1: Test [3]	Case 1: Retest	Case 2: Test	Case 2: Retest
LEFT FRONTAL				
L MFG (11)	-	-	-26,48,-14 (6.1)	-
L SFG (11)	-	-	-14,50,-18 (5.0)	-
	-	-	-20,60,-10 (4.8)	-
L SFG (8)	-	-	-6,18,52 (4 .9)	-
L SFG SMA (6)	-	-	-	-10,9,58 (5 .1)
L MedFG (8)	-	-	-4,28,46 (6 .6)	-8,26,48 (5 .2)
	-	-	0,26,47 (6.5)	-
L MedFG (10)	-	-6,56,-6 (5.0)	-	-
LEFT TEMPORAL				
L TFG (36)	-38,-38,-25 (7.5)	-	-	-
L TFG (37)	-44,-61,-14 (7.1)	-	-28,-51,-18 (7.3)	-42,-61,-7 (4.8)
	-	-	-36,-45,-13 (6.7)	-36,-63,-19 (4.6)
L TFG (19)	-	-46,-70,-10 (inf)	-	-
L MTG (21)	-61,-39,-8 (5.8)	-	-	-
L MTG (39)	-	-	-	-48,-60,8 (4.5)
L STG (39)	-	-	-	-32,-55,32 (4.1) *
LEFT PARIETAL				
L SupraMarg (40)	-	-	-42,-41,37 (3.5)*	-
RIGHT FRONTAL				
R IFG (9)	44,4,31 (7.2)	48,7,25 (6.3)	-	50,19,27 (4.64)*
R IFG (44)	44,16,5 (4.3) *	-	-	-
R IFG (45)	-	-	-	51,24,10 (3.6)*
R IFG (47)	40,15,-6 (5 .2)	-	28,27,-8 (5 .6)	28,27,-6 (4 .8)
	-	-	38,26,-15 (4 .9)	46,18,1 (3.2) *
R MFG (46)	40,34,22 (5.6)	-	44,19,21 (7.7)	42,18,19 (5. 1)
	-	-	-	50,32,9 (3.7) *
R MFG (10)	38,48,-4 (6 .4)	-	38,39,13 (6.6)	40,39,13 (4.1) *
	34,46,-4 (6 .3)	-	24,54,-11 (6 .4)	-
R MFG (6)	30,-11,45 (inf)	32,-11,45 (7.1)	42,14,49 (inf)	38,12,47 (inf)
	-	42,-3,53 (7.1)	26,3,62 (5.0)	-
R MFG (11)	-	-	46,48,-17 (4 .9)	38,50,-19 (6 .5)
R MedFG (6)	8,-19,51 (6 .9)	8,-19,51 (6.3)	2,29,35 (5.6)	-
R MedFG (10)	-	4,58,-4 (5.6)	-	-
	-	4,60,3 (5.0)	-	-
R Cing (32)	-	6,6,47 (5.6)	-	8,34,26 (4.3)*
R SFG (6) (** =SMA)	-	24,-8,67 (5.8)	2,16,54 (6.5) **	6,18,54 (6.3) **
R SFG (11)	-	-	26,44,-17 (6 .5)	28,55,-18 (5.1)
	-	-	16,63,-16 (5 .5)	20,44,-17 (4.6)*
R MFG (9)	44,27,26 (6 .0)	48,27,34 (5.7)	59,21,28 (4.9)	36,17,36 (4.2)*
RIGHT TEMPORAL				
R TFG (37)	38,-59,-16 (inf)	38,-59,-16 (7.8)	34,-59,-11 (5.8)	36,-51,-15 (5.6)
	42,-61,-7 (7.6)	-	-	-
R STG (38)	50,15,-7 (4 .3) *	-	-	-
RIGHT PARIETAL				
R AngG (39)	-	-	34,-55,34 (5 .5)	32,-55,36 (4.4)*
	-	-	-	34,-57,32 (4.4)*

[1] P < .001 uncorrected; Family-Wise Error Rate < .05 corrected ; (* = False Discovery Rate < .05 corrected)
[2] Numbers in parentheses refer to Brodmann areas. MedFG=Medial Frontal Gyrus; TFG=Temporal Fusiform Gyrus; MTG=Middle Temporal Gyrus; MFG=Middle Frontal Gyrus; SFG=Superior Frontal Gyrus; **=SMA; SMA=Supplementary Motor Area; SupraMarg=supraMarginalGyrus; AngG =angular Gyrus; Cing= Cingulate
[3] Numbers refer to stereotaxic coordinates x, y, z from Talairach & Tournoux (1988) converted from MNI space (Brett, 2003); numbers in parentheses refer to Z scores

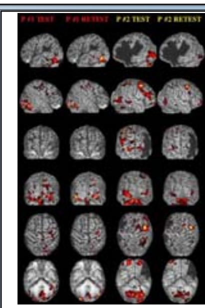


Figure 5. Cortical activation maps for P #1 and P #2 during TEST and RETEST. Areas activated (p<.001 uncorrected, for display) during the nonverbal semantic decision task on each participant's reconstructed lateral brain images.

Figure 6. P #1 during TEST and RETEST. Crosshair is on R med FG (BA 6). During TEST, more voxels activated (BA 6) than during RETEST, compatible with task familiarity (Buchel,Friston, 2002).

Figure 7. P #2 during TEST and RETEST. Crosshair is on R IFG (BA 47). During TEST, more voxels activated (BA 47) than during RETEST, compatible with task familiarity (Blasi et al., 2002).

CONCLUSIONS

1. Moderate-severe nonfluent aphasia patients can participate reliably in fMRI language studies. Intrasubject reliability in BOLD fMRI responses was established in two participants during two separate, identical semantic judgment tasks on the same day. For each patient, in ROIs activated during TEST, fewer voxels were activated in these ROIs during RETEST, compatible with task familiarity previously seen in fMRI studies with normals and aphasia patients (Buchel & Friston, 2002; Blasi, et al., 2002).
2. P #2 ("best response" to C-ViC) had activation in more LH regions, e.g., L SMA; and perilesional areas, e.g., L supramarginal gyrus (BA 40), than did P#1 ("moderate response" to C-ViC).
3. Our fMRI results with severe aphasia patients post- C-ViC training support those of other treatment studies, where some LH and perilesional activation was compatible with better aphasia recovery in patients post-speech therapy intervention (Leger, Demonet et al., 2002; Cornelissen, Laine, et al., 2003).

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