Voxel-lesion symptom mapping of coarse coding and suppression deficits in right hemisphere damaged patients

Several accounts of narrative comprehension deficits in adults with right hemisphere damage (RHD) focus on the basic comprehension processes of coarse semantic coding (CC) and suppression (SUP)[1,2]. CC activates wide-ranging aspects of word meaning, independent of the surrounding context. In RHD, CC deficits impair processing of more remote meanings/features of lexical-semantic representations (e.g., "rotten" as a feature of "apple")[3]. The normal SUP process reduces mental activation of concepts that become contextually incompatible. SUP impairment in RHD is indexed by prolonged processing interference from contextually-inappropriate interpretations (e.g., the "ink" meaning of "pen," in "He built a pen")[4,5]. Adults with RHD may have deficits in CC, SUP, both, or neither[6].

Voxel-based lesion symptom mapping was used to identify right hemisphere (RH) anatomical correlates of CC and SUP deficits. Lesion-deficit correspondence data should help predict which RHD patients have which deficits and may be candidates for a deficit-focused treatment approach that simultaneously improves narrative comprehension[7-9]. The Bilateral Activation, Integration, and Selection (BAIS) framework of language processing[10] suggests some basic hypotheses[1]. CC, related to the *activation* component, is hypothesized to involve posterior MTG and STG[10,11]. SUP, related to the attentionally-driven *selection* component, modulates lexical-level activation and message-level semantic integration to narrow representations to those most relevant to a comprehender's goal. Selection is strongly associated with left IFG[e.g,12] but RH IFG also is crucial for semantic filtering and selection[13,14], especially for information more strongly active in the RH[15]. Basal ganglia circuits are likely involved, as well[13,16].

Method

Participants (see Table 1) were 20 adults with unilateral RH CVA. All were right-handed, monolingual, native speakers of American English who passed a hearing screen.

Behavioral data. Priming of target semantic features or meanings of sentence-final nouns was assessed with lexical decision tasks. The tasks were auditorily-presented, requiring participants to indicate via button press (Yes/No) whether a target phoneme string was a real word. About half the targets were nonwords. Both tasks included short (175 ms) and long (1000 ms) intervals between sentence and target. Accuracy and ms response times (RT) were recorded.

For CC, 15 semantically-neutral sentences, ending with common unambiguous nouns (e.g., "He has an apple"), were paired with 3 types of real-word targets. CC-relevant targets reflected weakly-related features consistent with a non-dominant representation of the noun (e.g., ROTTEN). Comparison targets reflected weakly-related features of the dominant representation (e.g., CRUNCHY). Unrelated words (e.g., FLUFFY), not expected to be primed by the nouns, were also included.

For SUP, 20 sentences ending in ambiguous nouns, and semantically-biased toward dominant meanings (e.g., "He trained the seal"), also were paired with 3 types of real-word targets. SUP targets were related to the subordinate meaning (e.g. TIGHTEN) and thus were candidates for suppression. Other targets words reflected the nouns' dominant meanings or were unrelated.

Primary dependent measures are based on RT ratios, calculated for accurate responses[2]. The CC-relevant index is $RT_{WeakNonDominant}/RT_{Unrelated}$ and for CC comparison targets it is $RT_{WeakDominant}/RT_{Unrelated}$. Larger ratios indicate a deficit, i.e., for CC, impaired priming of remote features. For SUP, the primary index is the SUP effectiveness ratio, calculated by subtracting RT ratios ($RT_{Subordinate}/RT_{Unrelated}$) for the long interval from those for short interval. Because smaller RT ratios indicate priming, a negative SUP effectiveness ratio signifies effective suppression (smaller short

[1]Space limitations preclude more complex hypotheses.
[2]Adults with RHD are always highly accurate on lexical decision tasks.

interval ratio, due to temporary activation of contextually-incompatible meanings, than long interval ratio, when that activation has been suppressed). A SUP effectiveness ratio closer to 0 indicates SUP deficit.

Neuroanatomical data. MRIs were obtained contemporaneously with behavioral testing, using a GE Signa 1.5T scanner. The coronal high-resolution volumetric SPGR sequence was the basis for analysis. Using MRIcron[17], the acquired files were converted to NifTi format and scalp stripped, and lesions were independently demarcated directly on coronal slices (refined on axial and sagittal slices) by multiple "drawers" blind to participants' symptoms. Between these drawers there were fewer than 8% discrepant voxels ($\geq$2 voxels away in 3D space[18]). An experienced stroke neurologist, also blinded, validated 25% of lesion drawings.

Using SPM8[19], these drawings were globally oriented to within 5^0 of an older brain template[20]. Then cost-function masking was used to delineate the lesion boundaries when calculating transformation parameters[21,22]. Segmentation and normalization were performed to warp each patient's scan onto the older brain template[20]. The same transformation matrix was then applied to the patient's lesion drawing.

The normalized lesion files, masked occipitally, were then entered with the behavioral measures into NPM to construct design matrices[17]. For each matrix, we ran a separate VLSM analysis, which builds a general linear model for each voxel using behavioral scores as continuous predictors[17,23]. Each VLSM analysis yielded a Brunner-Munzel z-score map[24-26], which was parceled and labeled by AAL (Automated Anatomical Labeling)[27]. Regions of labeled anatomical structures, MNI coordinates, voxel size and Brodmann Areas labels were generated. A specific region is considered significant only if (1) the *q*-values of all the voxels (FDR controlled for multiple comparisons) are smaller than 0.05; and (2) the cluster is larger than 15 voxels.

Results

Table 2 summarizes the behavioral data. Table 3 and Figures 1 and 2 present the VLSM results, including MNI coordinates and associated Brodmann areas (BA).

Results for CC-relevant RT ratios are evaluated in relation to results for the comparison ratios. At the short interval, poor CC is associated uniquely with lesions in posterior Middle Temporal gyrus (MTG; BA 21,39). Also implicated are lesions in a dorsolateral portion of posterior Middle Frontal gyrus (MFG) in BA 46, and in lenticular nuclei. Comparison ratios uniquely implicate Superior Temporal gyrus (STG; BA 22,41,42), anterior lateral caudate, anterior medial insula (BA 13,14) and an extension of Inferior Frontal gyrus (IFG) into Orbitofrontal cortex (BA 11). Poor long-interval maintenance of CC activation involves lesions in anterior STG/temporal pole (BA 38) and dorsolateral (BA9,46) and prefrontal lesions extending into medial Superior Frontal gyrus (SFG) in BA 10, including white matter. Long-interval comparison ratios uniquely involve putamen. IFG pars opercularis and triangularis (BA 44,45) are significant in both conditions.

Poor SUP Effectiveness is related to large lesion clusters in corticostriatal circuits, including portions of IFG (BA 45,47), STG/Temporal pole (BA 22,38) and underlying white matter, insula (BA 13,14), and caudate, putamen, and globus pallidus.

Discussion and Implications

Early activation of remote features of lexical-semantic representations uniquely depends on posterior RH MTG, as hypothesized, but also on RH dorsolateral prefrontal cortex (DLPFC). Longer-term maintenance of this activation is related to more medial/posterior/inferior DLPFC. DLPFC involvement may suggest a greater need for RH post-activation/post-retrieval refreshing, monitoring, or evaluation[28,29] of semantic features that are particularly remote from a dominant representation than less remote features. DLPFC is connected to CC-relevant posterior temporal/parietal regions, as well. Lesions extending into RH temporal pole also impair maintenance of remote-feature activation, perhaps due to its representation-inconsistent nature[30] or to disruption of multimodal semantic memory representations[31].

As hypothesized, effective suppression of contextually-incompatible meanings depends on RH corticostriatal circuits[13,14,16] important for resolving lexical ambiguity[13]. Beyond IFG and basal ganglia, though, the integrity of RH anterior STG and underlying white matter is important, perhaps due to a role in processing representation-incompatible material[30]. If information is not registered as context-inconsistent, suppression would not be triggered.

Implications will be discussed for diagnostic hypotheses and treatment approaches.

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Table 1. Demographic and clinical characteristics of study participants

Characteristics	
Age (years)	65.2(11.3)
Mean (SD)	42-78
Range	
Sex	12 female
	8 male
Education (years)	
Mean (SD)	13.5 (2.4)
Range	10-20
Months post-onset	
Mean (SD)	52.5 (54.7)
Range	4-167
Peabody Picture Vocabulary Test-R[a]	
(Maximum = 175)	
Mean (SD)	156.7(11.2)
Range	134-170
Behavioural Inattention Test[b]	
(Maximum = 146; neglect cutoff = 129).	
Mean (SD)	137.3 (9.4)
Range	104-146
Auditory Working Memory for Language[c]	
Word recall errors	
(Maximum = 42)	
Mean (SD)	14.0 (7.0)
Range	1-27
Judgment of Line Orientation[d]	
(Maximum (age/gender corrected) = 35)	
Mean (SD)	19.8 (5.5)
Range	4-28
Visual Form Discrimination[e]	
(Maximum = 32; cutoff = 23)	
Mean (SD)	27.5 (3.5)
Range	23-32

ABCD[f] Story Retell (Maximum = 17)	
Immediate	
Mean (SD)	13.4(2.4)
Range	7-17
Delayed	
Mean (SD)	12.8 (3.0)
Range	5-17

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Table 2. Descriptive statistics for behavioral response time ratios

	Mean (SD)	Range
Coarse coding		
WeakNonDom/Unrelated		
Short interval	1.23 (0.22)	0.97-2.05
Long interval	1.39 (0.57)	1.00-3.68
WeakDom/Unrelated		
Short interval	1.20 (0.19)	0.89-1.61
Long interval	1.32 (0.24)	0.92-1.80
Suppression		
Subordinate/Unrelated		
Short interval	1.04 (0.16)	0.79-1.32
Long interval	1.11 (0.15)	0.88-1.39
Suppression effectiveness	-0.07 (0.15)	-0.58 - 0.08

Note. WeakNonDom/Unrelated = coarse-coding-relevant index = response times for weak features of nondominant representations / response times for unrelated trials.

WeakDom/Unrelated = comparison-relevant index = response times for weak features of dominant representations / response times for unrelated trials.

Subodinate/Unrelated = response times for subordinate meaning trials / response times for unrelated trials.

Suppression effectiveness = index of suppression function = ((Short interval Subordinate/Unrelated) – (Long interval Subordinate/Unrelated)).

Table 3. Right hemisphere areas significant for coarse coding and suppression reaction time indices and suppression effectiveness.

CC indices	**Main significant anatomical areas**	**MNI coordinates, Brodmann Areas**	**SUP Indices**	**Main significant anatomical areas**	**MNI coordinates, Brodmann Areas**
WeakNonDom/UN short interval	posterior Middle Temporal gyrus Inferior Frontal gyrus (pars triangularis and opercularis) Inferior (pars opercularis) and posterior middle Frontal gyrus anterior lateral and medial Putamen lateral Globus pallidus	(36,-63,16) BA 21 (43,24,19) BA 44, 45, 46 (43,6,27) BA 44, 46 (26, 2, 12) (24,-14,-2)	SUP Effec	Inferior Frontal (pars triangularis and opercularis) and Superior Temporal gyri and Insula rostral Temporal pole white matter, rostral Superior Temporal and Middle Temporal gyri Caudate, Putamen, Globus pallidus	(39,16,-15) (43,19,-16) BA 45,47, 22,13,14 (43,19,-16) (46,16,-16) BA 38 (23,-8,23) (23,-8,23)
WeakDom/ UN short interval	Superior Temporal gyrus Inferior Frontal gyrus (pars triangularis, orbitalis, and opercularis) anterior lateral Caudate anterior medial Insula	(49,-31,5) BA 22, 41, 42 (27,19,22) (31,23,-22) BA 11, 44, 45, 47 (22,-9,15) (27,-19,22) BA 13, 14	SUB/ UN short interval	Inferior Frontal gyrus (pars triangularis) Temporal pole, anterior Superior Temporal gyrus posterior Middle Frontal gyrus anterior medial Insula Lenticular nuclei: anterior lateral Putamen, posterior medial and anterior lateral Globus pallidus	(38,17,22) BA 45 (34,3,-19) (39,14,-19) BA 22, 38 (27,16,29) BA 9, 46 (38,1,-2) BA 13, 14 (26,4,15)
WeakNonDom/UN long interval	Temporal pole, anterior Superior Temporal gyrus (most rostral part) Inferior Frontal gyrus (pars triangularis) Dorsolateral Prefrontal area and medial Superior Frontal gyrus	(34,3,-19) BA 38 (38,17,22) BA 45 (26,4,25) BA 9, 10, 46	SUB/ UN long interval	Inferior Frontal gyrus (pars triangularis and opercularis) and posterior Middle Frontal gyrus Inferior Frontal gyrus (pars orbitalis) and Insula anterior Inferior Parietal area anterior Middle Temporal gyrus	(55,27,3) (48,23,20) BA 44, 45, 46 (23,15,-18) BA 47, 13, 14 (34,-48,34) BA 40 (36,-65,11) BA 21
WeakDom/ UN long interval	Inferior Frontal gyrus (pars triangularis) Putamen	(38,17,22) BA 45 (25,4,25) (30,-3,10)			

Note: CC=Coarse coding; WeakNonDom=weak semantic feature target, related to nondominant representation of noun (primary index of CC); UN=unrelated target; WeakDom=weak semantic feature target, related to dominant representation of noun (comparison index for CC); SUP=Suppression; SUP Effec=suppression effectiveness=response time ratio difference score (SUB/UN Short Interval) – (SUB/UN Long interval); primary index of suppression); SUB=subordinate meaning target; MNI=Montreal Neurological Institute; BA=Brodmann Area.

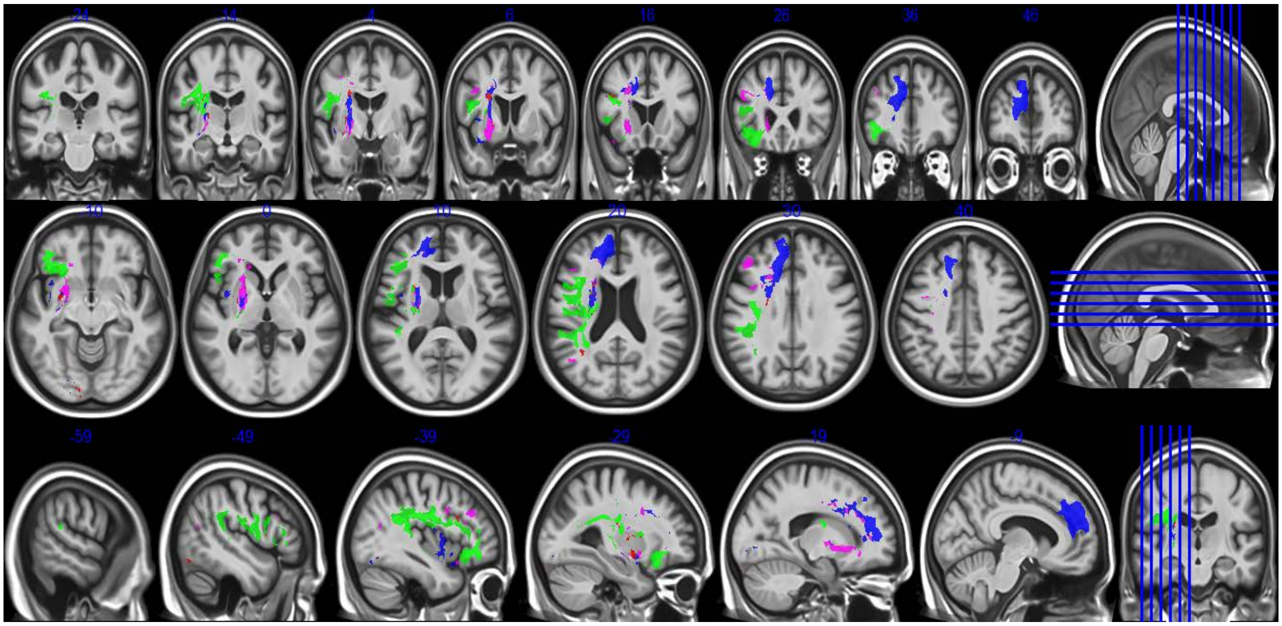

Figure 1. Clusters of significant right hemisphere lesion voxels related to coarse coding (CC) indices in VLSM models, registered on older brain template. All indices are reaction time ratios. From top panel to bottom panel: coronal view, axial view and sagittal view. Violet: WeakNonDominant/Unrelated (CC index) at Short interval; green: WeakDominant/Unrelated (comparison index) at Short interval; blue: WeakNonDominant/Unrelated at Long interval; red: WeakDominant/ Unrelated at Long interval. At the Short interval, poor CC is uniquely related to posterior Middle Temporal gyrus, posterior Middle Frontal gyrus (dorsolateral prefrontal cortex), and lenticular nuclei. The Short interval comparison index is uniquely associated with the Superior Temporal gyrus, anterior lateral Caudate, anterior medial Insula, and Inferior Frontal extension into Orbitofrontal cortex. At the Long interval, poor CC uniquely involves anterior Superior Temporal gyrus (temporal pole) and dorsolateral prefrontal areas extending into medial Superior Frontal gyrus (including white matter). The Long interval comparison index is only uniquely related to a cluster involving the putamen.

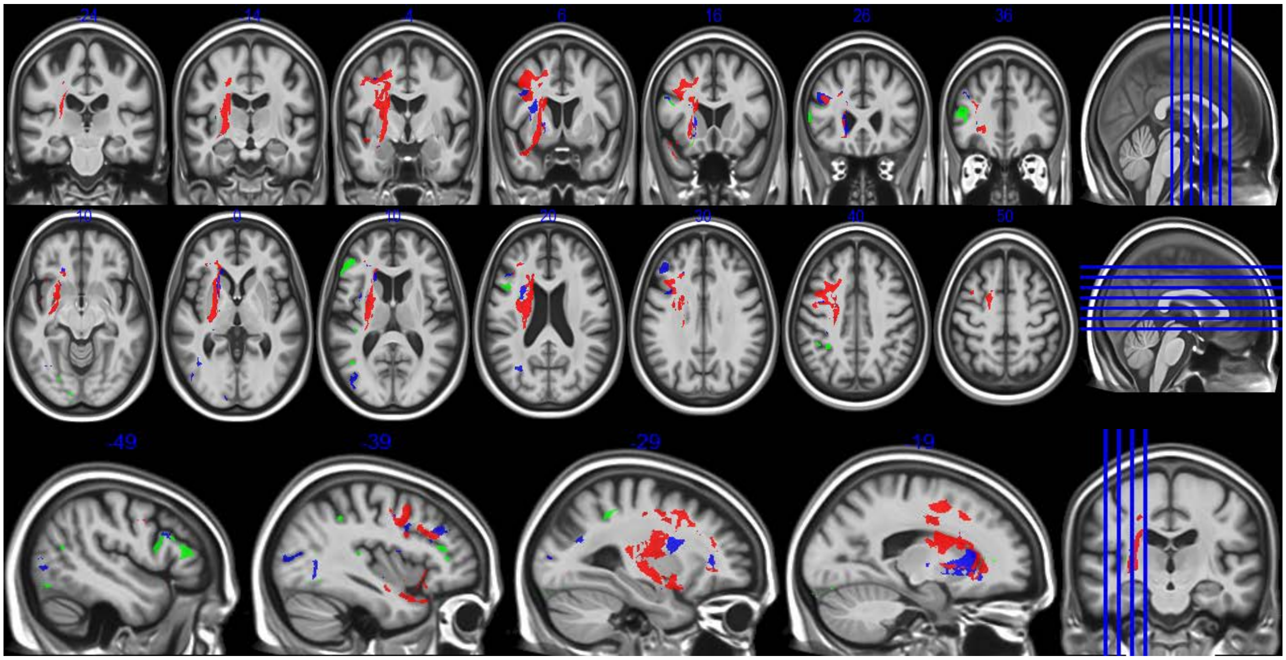

Figure 2. Clusters of significant right hemisphere lesion voxels related to suppression (SUP) indices in VLSM models, registered on older brain template. From top panel to bottom panel: coronal view, axial view and sagittal view; Blue: reaction time ratio Subordinate/Unrelated, Short interval; Green: reaction time ratio Subordinate/Unrelated, Long interval; Red: Suppression effectiveness, computed as Subordinate/Unrelated in Short interval - Subordinate/Unrelated in Long interval. Poor suppression effectiveness is related to large lesion clusters in corticostriatal circuits, including portions of Inferior Frontal and Superior Temporal gyri and Insula, Temporal pole, white matter underlying rostral Superior/Middle Temporal gyri, Caudate, Putamen, and Globus pallidus.