Supporting Information

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SI Text

Lesion Volume and Cognitive Impairment. Lesion volume is known to be related to cognitive dysfunction, with the unsurprising finding that more volume tends to cause more impairment (1–4). We evaluated the relationship between lesion volume and overall cognitive impairment in the target and control groups using correlation tests (Pearson's r). Log_{10}-transformed lesion volume was correlated with mean cognitive impairment ratings (i.e., across all domains) for the target group ($r = 0.703$, $P = 0.001$), but not for the control group ($r = 0.176$, $P = 0.605$) (Fig. S6, *Lower*). These correlations were only marginally different by Fisher's Z test (one-tailed test for target > control, $Z = 1.61$, $P = 0.053$), but this is likely related to the relatively small sample sizes. The discrepancy is intriguing and may reflect the importance of regions near target locations for many different cognitive processes.

Involvement of Broca's Area. Target locations in the left anterior insula (L aIns) and left posterior middle frontal gyrus (L pMFG) were near Broca's area, and many subjects in the target group had impairments in the language domain. To explore this issue in more detail, we defined an anatomic region of interest (ROI) that allowed us to determine whether patients in our target group had lesions that intersected the classically defined Broca's area (i.e., the pars triangularis and pars opercularis, Brodmann's areas 44 and 45). Six of 19 patients in the target group had lesions that encroached on Broca's area (mean proportion of ROI damage, 0.327 ± 0.303), whereas the remaining 13 patients had lesions that spared Broca's area entirely. Target group patients with lesions sparing Broca's area were still notably impaired relative to the control group. Moreover, the results for the patients with lesions sparing Broca's area were not consistent with the null hypothesis of no impairment (for all, Wilcox $Z > 3.0$, $P < 0.05$). In addition, target group patients with no impairment in verbal functions and/or language skills still had widespread and severe cognitive deficits (Fig. S4 and Table S4).

1. Bagher-Ebadian H, et al. (2011) Predicting final extent of ischemic infarction using artificial neural network analysis of multi-parametric MRI in patients with stroke. *PLoS ONE* 6(8):e22626.
2. Beaulieu C, et al. (1999) Longitudinal magnetic resonance imaging study of perfusion and diffusion in stroke: Evolution of lesion volume and correlation with clinical outcome. *Ann Neurol* 46(4):568–578.
3. Jokinen H, et al. (2005) White matter hyperintensities as a predictor of neuropsychological deficits post-stroke. *J Neurol Neurosurg Psychiatry* 76(9):1229–1233.
4. Lövblad KO, et al. (1997) Ischemic lesion volumes in acute stroke by diffusion-weighted magnetic resonance imaging correlate with clinical outcome. *Ann Neurol* 42(2):164–170.

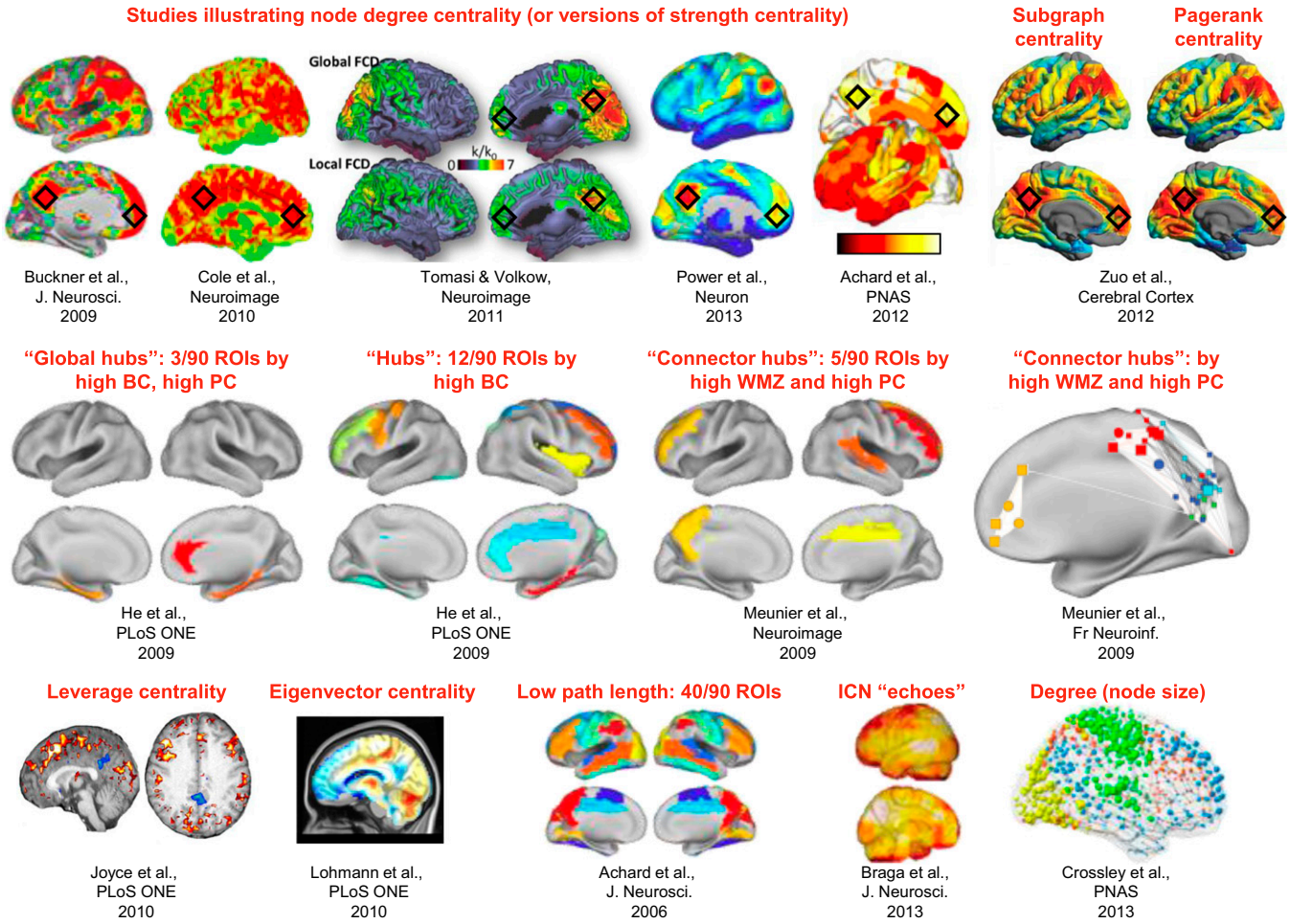

Fig. S1. Locations of hubs in various publications. Note the diversity of network node definitions (e.g., voxels, parcels, random subparcellations of parcels), the various measures of node importance, the variety of locations described as "hubs," and the convergent identification across many centrality measures of the posterior cingulate and precuneus as a hub. Diamonds on several brains designate the control locations. Figures in the middle row and bottom row, center (Achard et al., 2006), were created based on tables presented in the original reports. All other images were used with permission (from top left): refs. 1–10.

1. Buckner RL, et al. (2009) Cortical hubs revealed by intrinsic functional connectivity: Mapping, assessment of stability, and relation to Alzheimer's disease. *J Neurosci* 29(6):1860–1873.
2. Cole MW, Pathak S, Schneider W (2010) Identifying the brain's most globally connected regions. *Neuroimage* 49(4):3132–3148.
3. Tomasi D, Volkow ND (2011) Functional connectivity hubs in the human brain. *Neuroimage* 57(3):908–917.
4. Power JD, Schlaggar B, Lessov-Schlaggar C, Petersen S (2013) Evidence for hubs in human functional brain networks. *Neuron* 79(4):798–813.
5. Achard S, et al. (2012) Hubs of brain functional networks are radically reorganized in comatose patients. *Proc Natl Acad Sci USA* 109(50):20608–20613.
6. Zuo XN, et al. (2012) Network centrality in the human functional connectome. *Cereb Cortex* 22(8):1862–1875.
7. Joyce KE, Laurienti PJ, Burdette JH, Hayasaka S (2010) A new measure of centrality for brain networks. *PLoS One* 5(8):e12200.
8. Lohmann G, et al. (2010) Eigenvector centrality mapping for analyzing connectivity patterns in fMRI data of the human brain. *PLoS One* 5(4):e10232.
9. Braga RM, Sharp DJ, Leeson C, Wise RJ, Leech R (2013) Echoes of the brain within default mode, association, and heteromodal cortices. *J Neurosci* 33(35):14031–14039.
10. Crossley NA, et al. (2013) Cognitive relevance of the community structure of the human brain functional coactivation network. *Proc Natl Acad Sci USA* 110(28):11583–11588.

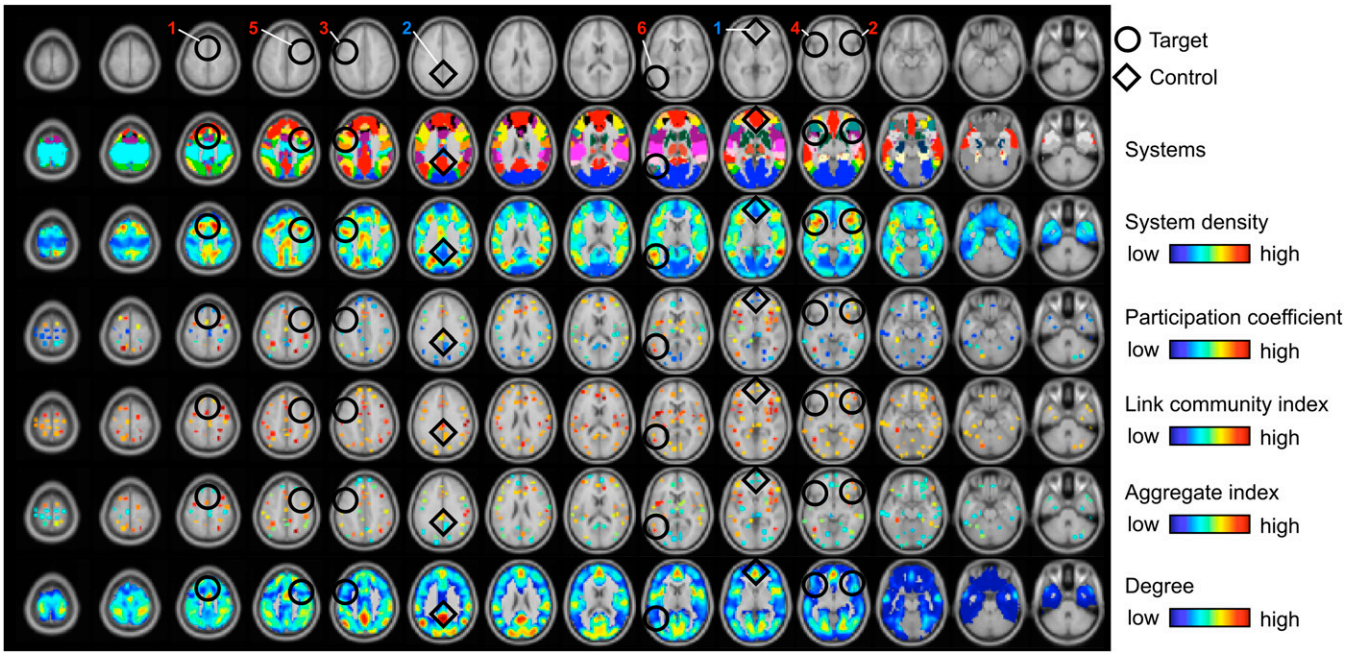

Fig. S2. Network properties leading to location selection. The top row shows slices from an MNI152 atlas image, with circles denoting approximate target locations and diamonds denoting approximate control locations. The next row shows the communities of Power et al. (1), followed by rows showing measures of system density, degree, and participation coefficient, all drawn from Power et al. (2); link community index; and an average of *z*-scored system density, participation coefficient, and link community index. This latter aggregate score was used to rank ROIs to select target locations (*Methods*). The last row shows degree centrality.

1. Power JD, et al. (2011) Functional network organization of the human brain. *Neuron* 72(4):665–678.
2. Power JD, Schlaggar BL, Lessov-Schlaggar CN, Petersen SE (2013) Evidence for hubs in human functional brain networks. *Neuron* 79(4):798–813.

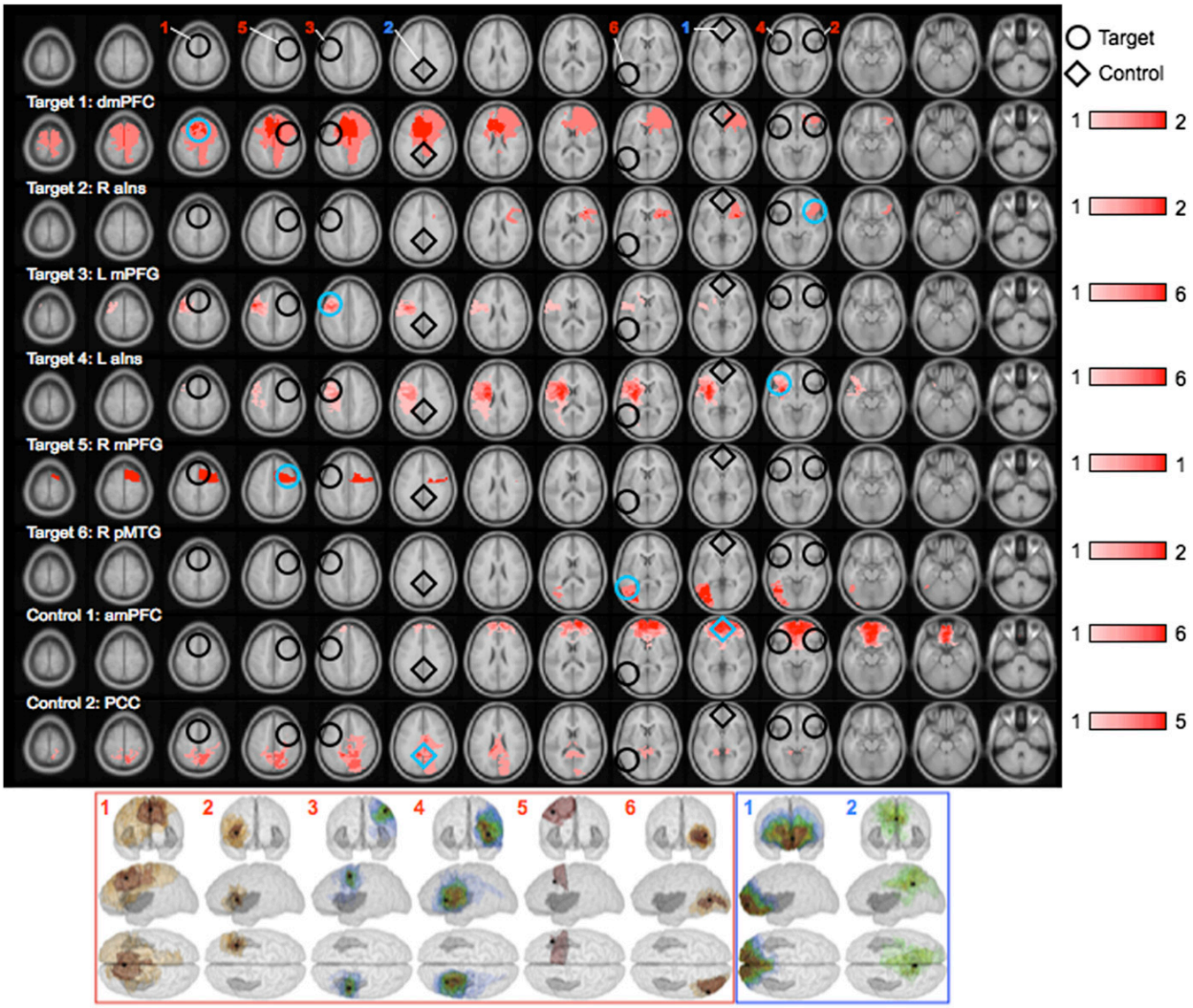

Fig. S3. Lesion locations. (*Upper*) Images of lesion overlap. Labels on color bars indicate the number of patients for each site. Note that the maximum lesion overlap at each location varies from 2–6. (*Lower*) Comparable images in glass brains.

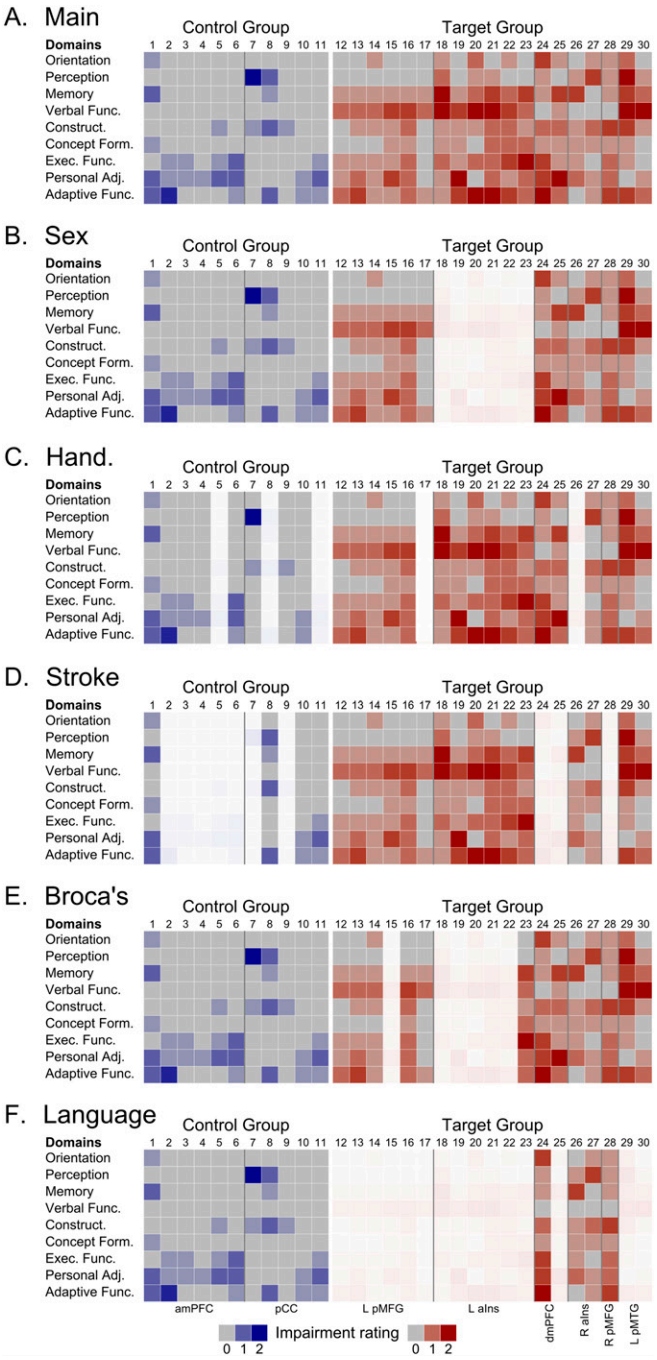

Fig. S4. Follow-up analyses controlling for demographic, attribute, and lesion variables, related to Fig. 2, *Right* and Table S4. (*A*) Reproduction of Fig. 2 for reference. In our main analysis, patients in the target group had greater impairment across more cognitive domains compared with patients in the control group. (*B–F*) Degree of impairment and profile agreement for the two groups after removing patients to control for several potentially confounding variables; censored cases are indicated by lighter colors. In each case, the relatively greater impairment of the target group is evident. (*B*) Sex. The L aIns target group was composed entirely of males, whereas other groups included both sexes (2 males and 4 females). The L aIns group was excluded from this analysis. (*C*) Hand (handedness). Several patients in the main analysis were not fully right-handed (+100; Table S1). This analysis was limited to fully right-handed patients only. (*D*) Stroke. Etiology was mixed in our control group, whereas most target cases suffered strokes. This analysis was limited to patients who suffered strokes only. (*E*) Broca's area. Six patients in the target group had lesions that infringed on an anatomically defined ROI for Broca's area. This analysis was limited to patients without damage to Broca's area. (*F*) Language. This analysis included only patients without impairment in Verbal Functions/Language Skills.

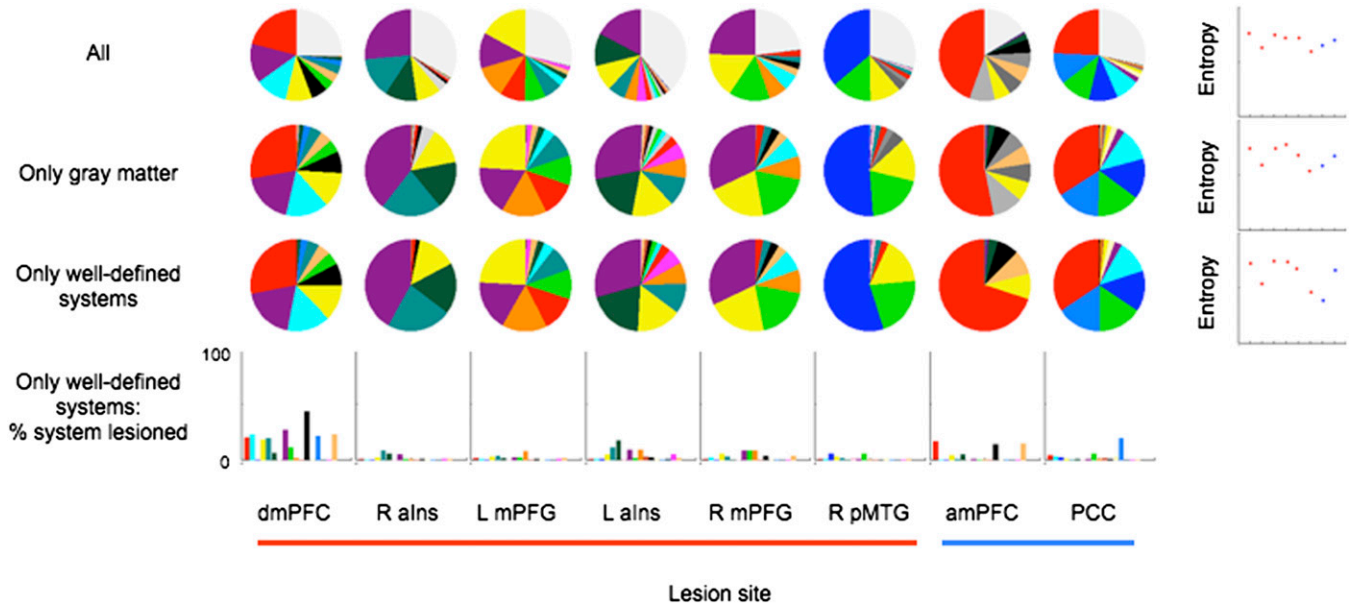

Fig. S5. Systems affected by each type of lesion, binned by location. Colors correspond to system labels used in Fig. 1. (*Upper*, *Left*) Pie charts showing the distribution of systems affected by each set of lesions, including all tissue types, excluding white matter, and excluding the "uncertain" modules (in the orbitofrontal and inferior temporal cortex, colored in shades of gray in Fig. 1). (*Right*) Plots of information-theoretic entropy, showing that the distribution of damage among systems is comparable and not highly disparate across control and target locations. (*Lower*) Proportion of each well-defined system lesioned, across subjects within a lesion location.

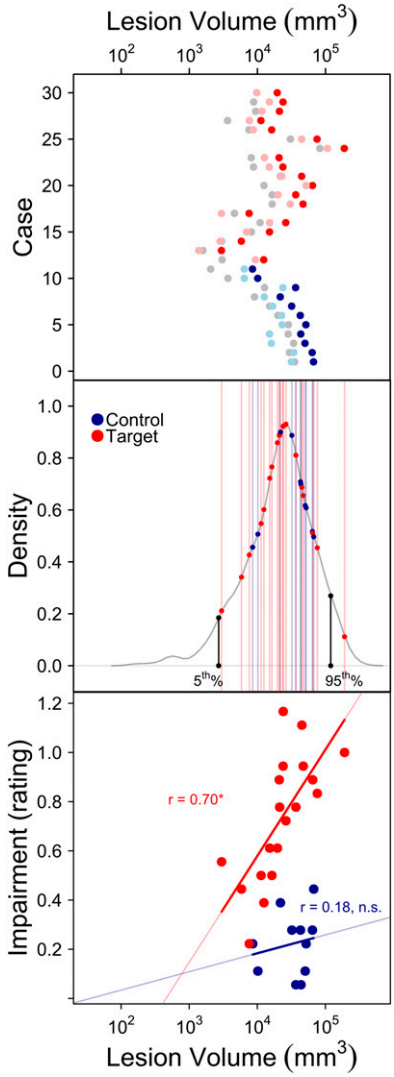

Fig. S6. Lesion volume and relation to cognitive impairment. Note that the abscissa common to all panels uses a log scale. (*Top*) Lesion volume for each case. Dark colored dots indicate total lesion volume, gray dots indicate estimated gray matter lesion volume, and light colored dots indicate estimated white matter lesion volume. (*Middle*) Volume of brain tissue lesioned in control and target patients, plotted in the context of several hundred Iowa Registry patient lesions. The gray line is related to frequency of cases with lesions within a range of volumes; black lines and points indicate the 5th and 95th percentiles in this distribution; colored points and lines indicate the volumes of lesions for the control patients (blue; $n = 11$) and main target patients (red; $n = 12$). Most control and target patients had lesion volumes that fell well within the typical range of the Iowa Patient Registry. On average, the control group had slightly larger lesion volumes compared with the target group. (*Bottom*) Relationship between lesion volume and overall mean neuropsychological impairment ratings for the main target ($n = 12$; red) and control ($n = 11$; blue) groups. In the target group, larger lesions were significantly correlated with greater overall cognitive impairment (*$P < 0.01$). In the control group, lesion volume was not significantly related to cognitive impairment.

Table S1. Demographic and lesion information for patients

Group	ROI	Patient ID	Sex	Age at lesion, y	Age at test, y	Chronicity	Etiology	Handedness	Education, y (category)	Occupation
Control	amPFC	1	F	33	38	67	Stroke (H)	+100	13 (2)	3
Control	amPFC	2	F	54	55	5	Resection (T)	+100	13 (2)	1
Control	amPFC	3	M	46	48	19	Resection (T)	+100	12 (2)	4
Control	amPFC	4	M	22	26	38	Resection (T)	+100	14 (2)	3
Control	amPFC	5	F	63	66	37	Resection (T)	−60	13 (2)	3
Control	amPFC	6	M	52	56	40	Resection (T)	+100	18 (3)	1
Control	pCC	7	F	38	40	28	Resection (A)	+100	19 (3)	1
Control	pCC	8	F	38	35	59	Stroke (H)	−100	12 (2)	2
Control	pCC	9	F	33	43	10	Resection (A)	+100	12 (2)	1
Control	pCC	10	F	46	34	11	Stroke (I)	+100	16 (3)	2
Control	pCC	11	F	34	47	12	Stroke (H)	−100	12 (2)	3
Mean				41.727	44.364	29.636			14.000	
SD				11.723	11.535	20.631			2.530	
Target	L pMFG	12	F	56	71	179	Stroke (I)	+100	12 (2)	3
Target	L pMFG	13	M	30	35	63	Stroke (I)	+100	12 (2)	2
Target	L pMFG	14	F	55	62	76	Stroke (I)	+100	12 (2)	2
Target	L pMFG	15	F	47	47	4	Stroke (I)	+100	12 (2)	2
Target	L pMFG	16	F	54	56	14	Stroke (I)	+100	12 (2)	5
Target	L pMFG	17	M	67	68	16	Stroke (I)	+85	12 (2)	4
Target	L aIns	18	M	73	75	25	Stroke (I)	+100	12 (2)	4
Target	L aIns	19	M	27	29	5	Stroke (I)	+100	12 (2)	4
Target	L aIns	20	M	56	58	23	Stroke (H)	+100	12 (2)	3
Target	L aIns	21	M	57	57	6	Stroke (I)	+100	11 (1)	5
Target	L aIns	22	M	52	53	15	Stroke (I)	+100	12 (2)	5
Target	L aIns	23	M	47	49	24	Stroke (I)	+100	16 (3)	1
Target	dmPFC	24	F	24	32	94	Resection (A)	+100	16 (3)	1
Target	dmPFC	25	M	50	50	11	Resection (T)	+100	11 (1)	5
Target	R aIns	26	M	49	64	171	Stroke (I)	+60	16 (3)	1
Target	R aIns	27	M	76	77	5	Stroke (I)	+100	12 (2)	2
Target	R pMFG	28	F	52	53	11	Resection (T)	+100	14 (2)	2
Target	L pMTG	29	F	66	67	9	Stroke (H)	+100	12 (2)	3
Target	L pMTG	30	F	59	65	77	Stroke (H)	+100	9 (1)	5
Mean				52.474	56.211	43.579			12.474	
SD				13.962	13.758	54.027			1.806	
Statistical difference			NS†	*	*	NS†			*	NS†
Statistic value			Fisher	2.197	2.282	0.194			2.224	Fisher
P value			0.1	0.028	0.022	0.846			0.026	0.264

Group means and SDs are presented at the bottom of each group section, and between-group tests are presented at the bottom of each column of numerical data. For convenience, some fields are reprinted from Table 1. Age at lesion represents the age of the patient at the time of brain injury, in years. Age at test represents the age of the patient at the time of research neuroimaging used for lesion tracing. Chronicity refers to the interval between lesion onset and neuroimaging study, in months. Fisher refers to Fisher's exact test, which yields only a *P* value. Handedness ranges from fully right handed (+100) to fully left handed (−100). Category represents educational attainment category (1, less than high school diploma; 2, high school diploma with some additional education; 3, college degree and beyond). Occupation refers to preinjury occupation categorized as US Bureau of Labor Statistics high-level aggregated Standard Occupational Classification (SOC) code; smaller numbers generally correspond to higher professional attainment. amPFC, anterior medial prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; L aIns, left anterior insula; L pMFG, left posterior middle frontal gyrus; L pMTG, left posterior middle temporal gyrus; NS, not significant; pCC, posterior cingulate cortex; R aIns, right anterior insula; R pMFG, right posterior middle frontal gyrus; Resection (A), resection of arteriovenous malformation; Resection (T), resection of benign tumor; Stroke (H), hemorrhagic stroke; Stroke (I), ischemic stroke.

*$P < 0.05$.

†NS, $P \geq 0.1$.

Table S2. Cognitive domains, with descriptions and/or characteristic examples

Cognitive domain	Description
Orientation/Attention	"...awareness of self in relation to one's surroundings..." "...abilities for focused behavior..."
Perception	"...involves active processing of the continuous torrent of sensations as well as their inhibition or filtering from consciousness."
Memory	"...the capacity to retain information and utilize it for adaptive purposes."
Verbal Functions/Language Skills	"...the two-way translation mechanism between...the organized manipulation of mental representations which constitutes thought, and the organized processing of verbal symbols and grammatical rules which constitutes sentences."
Construction/Motor Performance	"...combines perception with motor response...has a spatial component."
Concept Formation/ Reasoning	"...quality or process of thinking more than the content..." "...thinking with a conscious intent to reach a conclusion."
Executive Functions	"...(1) volition; (2) planning and decision making; (3) purposive action; and (4) effective performance."
Personal Adjustment/ Emotional Function	"...common direct effects of brain injury on personality are emotional dulling, disinhibition, diminution of anxiety with associated emotional blandness or mild euphoria, and reduced social sensitivity."
Adaptive Functions	"The usual criterion of good outcome for younger adults...is return to gainful employment." "For older people...degree of independence, self-care, and whether the patient could return home rather than to a care facility."

For each domain, the following rating scale was used: 0 = no impairment, meaning no significant impairment; 1 = moderate impairment, neuropsychological performance 1.5–2 SD below normative expectations and some effect on activities of daily living; 2 = severe impairment, neuropsychological performance at least 2 SD and typically ≥3 SD below normative expectations that substantially affect activities of daily living. Quotations describing each domain were drawn (whenever available) from corresponding chapter introductions in Lezak et al. (1), and from the main text of the chapter otherwise.

1. Lezak MD, Howieson DB, Bigler ED, Tranel D (2012) *Neuropsychological Assessment* (Oxford Univ Press, New York).

Table S3. Average ratings of impairment for each group in each cognitive domain and tests of between-group differences (related to Fig. 2)

	Target		Control			
Cognitive domain	Mean	SD	Mean	SD	Wilcox *Z*	*P* value
Orientation/Attention	**0.342**	**0.443**	0.045	0.151	2.148	0.032*
Perception	**0.395**	**0.567**	0.273	0.647	1.227	0.220
Memory	**0.895**	**0.542**	0.136	0.323	3.724	<0.001*
Verbal Functions/Language Skills	**1.132**	**0.742**	0.000	NA	120.0	<0.001*
Construction/Motor Performance	**0.711**	**0.419**	0.227	0.344	2.908	0.004*
Concept Formation/Reasoning	**0.421**	**0.344**	0.045	0.151	3.058	0.002*
Executive Functions	**0.737**	**0.537**	**0.273**	**0.344**	2.447	0.014*
Personal Adjustment/Emotional Functions	**0.842**	**0.602**	**0.545**	**0.416**	1.257	0.209
Adaptive Functions	**1.105**	**0.591**	**0.455**	**0.522**	2.690	0.007*
Overall	**0.731**	***0.040***	**0.222**	***0.046***	4.161	<0.001*

Impairment scores (0 = no impairment, 1 = moderate impairment, 2 = severe impairment) are summarized and compared for the target and control groups. In seven of the nine cognitive domains and in overall impairment, the target group was significantly more impaired than the control group. Scores in bold type were significantly greater than 0 ($P < 0.05$), whereas the others were not. Italicized entries at the bottom of each SD column indicate SEM for the overall impairment score. For the Verbal Functions domain, the entire control group was scored as normal, and so a 1-sample test vs. $\mu = 0$ was used instead (underlined).
*$P < 0.05$.

Table S4. Full statistical summary of follow-up analyses controlling for demographic, attribute, and lesion variables (related to Fig. 2)

Variable	Limited	Sex	Handedness	Education	Age at lesion	Age at test	Chronicity	Etiology	Broca	Language
Domain target, *n*	7	13	17	19	19	19	19	16	13	4
Control, *n*	11	11	8	11	11	11	11	4	11	11
Orientation/Attention	0.007*	0.046*	0.053†	0.419	0.389	0.477	0.049*	0.575	0.046*	0.011*
	(2.717)	(1.997)	(1.934)	(0.808)	(0.861)	(0.710)	(1.968)	(0.560)	(1.997)	(2.528)
Perception	0.024*	0.253	0.173	1.000	0.682	0.714	0.341	0.592	0.253	0.026*
	(2.253)	(1.143)	(1.363)	(< 0.001)	(0.409)	(0.366)	(0.952)	(0.536)	(1.143)	(2.219)
Memory	0.004*	0.001*	0.001*	0.001*	0.001*	0.001*	0.001*	0.094†	0.001*	0.051†
	(2.850)	(3.254)	(3.266)	(3.459)	(3.250)	(3.249)	(3.410)	(1.676)	(3.322)	(1.953)
Verbal Functions/	0.021*	0.001*	0.001*	< 0.001*	0.001*	0.001*	< 0.001*	0.006*	0.001*	NA
Language Skills	(2.303)	(3.309)	(3.439)	(3.766)	(3.272)	(3.206)	(3.739)	(2.735)	(3.317)	NA
Construction/	0.002*	0.010*	0.001*	0.034*	0.021*	0.024*	0.003*	0.107	0.010*	0.010*
Motor Performance	(3.038)	(2.562)	(3.375)	(2.126)	(2.303)	(2.259)	(2.938)	(1.612)	(2.562)	(2.582)
Concept Formation/	0.002*	0.010*	0.009*	0.069†	0.061†	0.078†	0.001*	0.165	0.009*	0.001*
Reasoning	(3.159)	(2.589)	(2.630)	(1.818)	(1.873)	(1.765)	(3.327)	(1.389)	(2.595)	(3.191)
Executive Functions	0.203	0.109	0.014*	0.094†	0.064†	0.067†	0.020*	0.037*	0.077†	0.140
	(1.274)	(1.602)	(2.462)	(1.675)	(1.851)	(1.829)	(2.330)	(2.088)	(1.766)	(1.476)
Personal Adjustment/	0.219	0.215	0.127	0.488	0.605	0.621	0.219	0.882	0.259	0.098†
Emotional Functions	(1.229)	(1.240)	(1.526)	(0.694)	(0.517)	(0.495)	(1.229)	(0.149)	(1.128)	(1.656)
Adaptive Functions	0.055†	0.034*	0.006*	0.015*	0.033*	0.031*	0.007*	0.376	0.023*	0.246
	(1.916)	(2.120)	(2.743)	(2.429)	(2.131)	(2.152)	(2.718)	(0.885)	(2.270)	(1.159)
Overall	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	0.009*	0.000*	0.004*
	(3.501)	(3.690)	(3.882)	(3.853)	(3.723)	(3.723)	(4.219)	(2.605)	(3.689)	(2.893)

Data are *P* values for nonparametric between-group tests and Wilcox *Z* values in parentheses. Follow-up analyses controlling for several variables revealed a broadly similar pattern as the main analysis with significant impairments of the target group always evident in two of nine cognitive domains. Abbreviations are as detailed in Fig. 2.

*$P < 0.05$.

†$P < 0.10$.