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Brain Connectivity of Lesions causing Post-stroke Depression

Na Young Kim[1], Sang Hoon Shin[1*], Yong Wook Kim[1†]

Yonsei University College of Medicine, Department & Research Institute of Rehabilitation Medicine[1]

Introduction

Depression is the most common neuropsychological sequela of stroke and an independent predictor of morbidity and mortality. Patients with focal brain lesions can yield insight into the causal neuroanatomical substrate underlying depression. However, localization of depression-causing brain region based on lesion location has led to inconsistent Results. Here, we test whether functional connectivity with each lesion location was related to depression along with a normative connectome, to identify underpinning brain regions or networks of post-stroke depression.

Method

Three independent post-stroke lesion data sets totaling 155 patients were included (Table 1). Lesions were manually segmented based on CT or structural MRI images, spatially normalized to MNI 152 space, and binarized. First, voxel lesion symptom mapping was performed to identify any lesioned brain voxels associated with depression (versus control lesions) using Bayesian Spatial Generalized Linear Mixed Model software. Second, functional connectivity between each lesion location and the rest of the brain was computed using resting state functional connectivity data from 1000 healthy subjects. Lesion network maps of depressed versus non-depressed subjects were statistically compared using a general linear model.

Result

Lesion location was not significantly associated with depression. In contrast to analyses focused on lesion location alone, lesion connectivity was significantly associated with depression. Specifically, a focal region in the left dorsolateral prefrontal cortex was significantly more connected to lesion locations associated with depression compared to control lesions. Negative functional connectivity (anti-correlation) to limbic regions was also predictive (Figure 1, Table 2)

Conclusion

Positive frontal connectivity and negative limbic connectivity were independent predictors of lesion-induced depression. These Results lend insight into the causal substrate of depression symptoms, identify patients at risk for post-stroke depression, and may help refine treatment targets for brain stimulation.

Table 1. Demographics and Clinical Characteristics

	Total Data	Gozzi et al, 2014	Corbetta et al, 2015	Kim et al, 2017
Total Subjects for Primary Analysis (Depressed/Control)	156 (29/127)	45 (7/38)	87 (14/73)	24 (8/16)
Mean age (stdev)	56.8 (15.6)	63.5 (13.5)	53.8 (11.0)	54.8 (17.7)
Sex (% M, % F)	89 M (57%), 67 F (43%)	29 M (64%), 16 F (36%)	45 M (52%), 42 F (48%)	15 M (63%), 9 F (37%)
Depression scale		Hospital Anxiety and Depression Scale	Geriatric Depression Score (Short Form)	Geriatric Depression Score (Long Form)
Depression threshold		HADS ≥ 11	GDSS ≥ 11	GDSS ≥ 17
Control threshold		HADS < 11	GDSS ≤ 5	GDSS ≤ 16

Table 2. Positive and negative peaks for lesion network mapping of depression

Cluster	Location	Voxels	Max T value	Max X	Max Y	Max Z
	Positive correlations					
1	Left middle frontal gyrus (left DLPFC)	612	4.68	-32	14	36
2	Right middle frontal gyrus (right DLPFC)	59	3.48	30	14	36
3	Left cerebral white matter (corpus callosum)	14	3.19	-2	-6	24
	Negative correlations					
1	Left cerebral white matter (medial forebrain bundle)	11	-3.39	-18	26	2
2	Right lateral ventricle (septal nuclei)	52	-3.33	2	18	4
3	Right cerebral white matter (right ventral striatum)	3	-3.05	20	14	-12

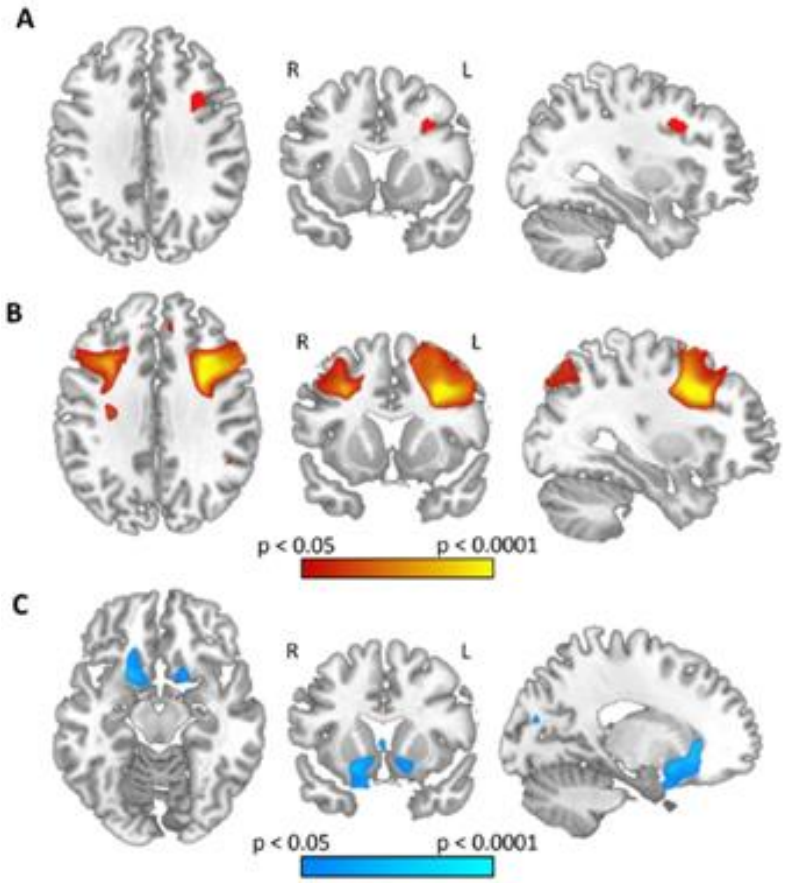

Figure 1. The connectivity profile of brain lesions causing depression. (A) A focal region in the left dorsolateral prefrontal cortex was significantly more connected to lesions causing depression than control lesions (whole brain voxel-level family-wise error corrected $p < 0.05$). Relaxing statistical threshold ($p < 0.05$, uncorrected) reveals a similar positive association in the right DLPFC (B) and identifies regions in limbic regions negatively associated with depression (C)