

Prefrontal asymmetry in depression? The long-term effect of unilateral brain lesions

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ABSTRACT

The proposal that a functional asymmetry in prefrontal cortex (PFC) may play a role in the pathophysiology of depression has sparked vigorous debate and investigation. One particularly contentious issue of clinical and theoretical importance is whether left PFC lesions are associated with the development of depression, and whether any such lesion-depression association is stable over time. To address this issue, we assessed the long-term depressive symptomatology of Vietnam veterans who had acquired left PFC lesions ($n = 21$), right PFC lesions ($n = 18$), non-PFC lesions ($n = 38$), or no brain lesions ($n = 31$) during the Vietnam War. Depressive symptoms were assessed at two different timepoints, approximately 15 and 35 years after lesion onset, respectively. There was no significant effect of PFC lesion laterality on overall depression severity at either timepoint. These data converge with previous stroke studies to suggest that PFC lesion laterality has no long-term systematic effect on vulnerability to depression.

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The prefrontal cortex (PFC) has long been recognized as a key brain area involved in the pathophysiology of depression. A recurrent theme in this field of research has been hemispheric laterality—whether a functional asymmetry between left and right PFC is related to mood and depression. This hypothesis has been supported by multiple convergent lines of evidence. PET and EEG studies have linked depression with pronounced hypoactivity in left (but not right) PFC [7,10], and studies of stroke patients have associated left (but not right) anterior lesions with increased risk for depression [12,13]. The lesion studies initially provided compelling evidence for a causal relationship between left PFC dysfunction and depression. However, the strength of this finding has been contested by multiple failed attempts at replication. Several reviews/meta-analyses of the stroke literature report no systematic effect of lesion location on poststroke depression [4,15,16], although other studies support a dynamic, time-dependent association between left anterior lesions and depression [3,11,14]. The long-term course of depression following unilateral PFC lesions is of clinical and theoretical importance, but this consideration has been largely neglected by poststroke depression studies, which rarely involve patient evaluations more than two years after lesion onset [4,3]. In the present study, we investigate the putative relationship between PFC lesion laterality and depressive symptomatology in a unique patient sample: war veterans

with focal brain damage from penetrating head injuries. Specifically, we address whether left PFC lesions are associated with greater depression severity than right PFC lesions, and whether the depressive symptomatology of each group is stable across decades.

We drew brain-injured participants from the Vietnam Head Injury Study (VHIS) registry, which includes American veterans who suffered brain damage from penetrating head injuries in the Vietnam War, as well as neurologically healthy Vietnam veterans. The VHIS has been organized in three phases. Phase 1 (1967–1970) was the initial enrollment; Phase 2 (1981–1984) included a clinical evaluation of depression; and Phase 3 (2003–2006) included a more comprehensive clinical evaluation of depression as well as CT brain imaging. Further details regarding the VHIS participants, including methods for visualizing and quantifying brain lesions, have previously been reported [8,9]. Subjects were eligible for the present study if they participated in Phases 2 and 3 clinical evaluations. From the pool of eligible VHIS veterans, we selected four participant groups based on lesion location: (1) those with unilateral lesions primarily involving right PFC (right PFC lesion group; $n = 18$), (2) those with unilateral lesions primarily involving left PFC (left PFC lesion group; $n = 21$), (3) those with unilateral lesions not involving PFC in either hemisphere (non-PFC lesion group; $n = 38$), and (4) those with no brain lesions (non-brain-damaged group; $n = 31$). Fig. 1 displays lesion locations for the two PFC lesion groups. Table 1 provides background data, collected during the Phase 3 assessment, for each group.

Depression severity for each participant was assessed during Phase 2 (1981–1984) and Phase 3 (2003–2006). During Phase 2,

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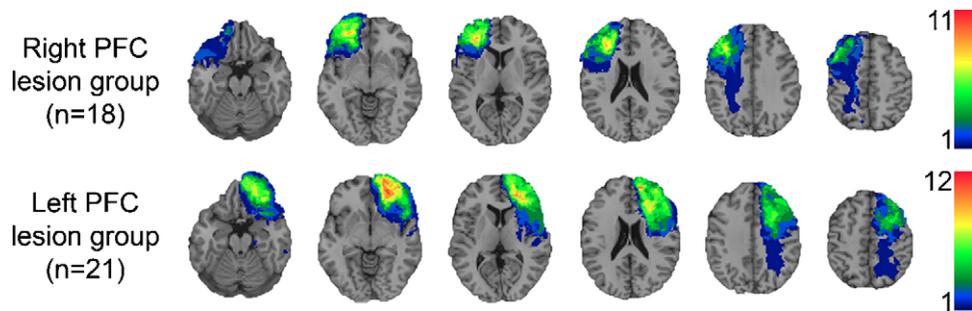


Fig. 1. Lesion overlap maps for the PFC lesion groups. Color indicates the number of overlapping lesions at each voxel. Regions of maximal overlap are depicted in red. Top row: lesion overlap for the right PFC lesion group, in transverse slices. Bottom row: lesion overlap for the left PFC lesion group, in transverse slices. In each slice, the right hemisphere is on the reader's left. The extent of PFC damage is similar in each group, but in opposite hemispheres. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 1

Background data.

Group	Age	Sex (%male)	Race (%Cauc)	Years Edu.	Lesion size	AFQT change	MMSE	Phys. Imp.	PTSD
Left PFC lesion (<i>n</i> = 21)	58.1 (3.2)	100	95	15.1 (2.8)	16.7 (35.1 ± 43.6)	-2.7 (14.9)	28.3 (3.1)	0.24	0.14
Right PFC lesion (<i>n</i> = 18)	58.2 (2.5)	100	94	14.2 (2.8)	18.9 (25.1 ± 21.3)	-11.5 (21.1)	28.8 (1.6)	0.11	0.06
Non-PFC lesion (<i>n</i> = 38)	58.9 (2.3)	100	87	15.4 (2.5)	16.1 (18.3 ± 16.5)	-9.3 (20.4)	28.6 (2.0)	0.18	0.13
Non-brain-damaged (<i>n</i> = 31)	58.1 (1.6)	100	87	14.6 (2.5)	n/a	3.4 (14.7)	29.1 (1.4)	0.03	0.19

Data in this table were collected at the time of the Phase 3 assessment. "Years Edu." refers to years of education. "Lesion size" refers to volume (in cm³). AFQT (Armed Forces Qualification Test) is a measure of basic intellectual function. "AFQT Change" refers to the difference between AFQT score at the time of enlistment (pre-injury) and the Phase 3 evaluation (post-injury). "MMSE" (Mini Mental State Exam) is a measure of basic cognitive function. "Phys. Imp." refers to physical impairment (paresis and/or voluntary movement abnormality) identified through a neurologist's examination. "PTSD" refers to meeting SCID-N/P criteria for current post-traumatic stress disorder. For "Age," "Years Edu.," "AFQT change," and "MMSE," data are presented as means with standard deviations in parentheses. For "Lesion size" median values are presented, followed by mean values ±SD. For "Phys. Imp." and "PTSD" data are presented as proportions of individuals in each group with the condition. Brain-injured groups did not significantly differ on any of the background variables (all *p* values >0.25).

depressive symptoms were assessed with the Beck depression inventory (BDI) [1]. The BDI is a 21-item self-report instrument for measuring the current severity of specific symptoms of depression. Participants rate each item on a scale of 0–3, with greater numbers indicating greater symptom severity. An overall BDI score (0–63) is derived by summing the severity ratings for each item. During Phase 3, depressive symptoms were assessed with the Beck depression inventory, second edition (BDI-II) [2] and the structured clinical interview for DSM-IV-TR Axis I disorders, non-patient edition (SCID-N/P) [6]. The BDI-II is similar to the original BDI in structure and scoring, although individual items were in some cases reworded or replaced. The SCID-N/P is a structured interview used for making DSM-IV Axis I diagnoses. A psychiatrist used the SCID-N/P to evaluate each participant for previous occurrence of major depressive disorder (MDD). The BDI/BDI-II and SCID-N/P assessments are complementary in that the BDI and BDI-II measure current (two weeks) symptom severity, whereas the SCID-N/P allows for detection of MDD at any point in the participant's lifetime. During the Phase 3 assessment the psychiatrist also ascertained whether the participants were currently prescribed antidepressant medication.

First we note that the three groups of brain-injured participants were matched on a number of variables that could be related to

depressive symptoms, including age, sex, race, education, lesion size, cognitive decline, basic cognitive function, physical impairment, and post-traumatic stress disorder (Table 1). The similarity among groups on these background variables allows a relatively straightforward interpretation of the effect of lesion location on the measures of depressive symptomatology. To assess the effect of PFC lesion laterality on overall depression severity, we compared Phase 2 BDI scores, Phase 3 BDI-II scores, prevalence of antidepressant medication, and lifetime prevalence of MDD for each of the four groups (left PFC lesions, right PFC lesions, non-PFC lesions, and non-brain-damaged; Table 2). There were no significant differences among groups on any of these individual measures (all *p* values >0.5). One-way ANOVAs indicate no significant group difference in Phase 2 BDI scores ($F_{3,104} = 0.37, p = 0.77$) or Phase 3 BDI-II scores ($F_{3,104} = 0.74, p = 0.53$). Chi-square frequency analyses indicate no significant group differences in lifetime prevalence of MDD ($\chi^2 = 1.4, p = 0.69$) or proportion of individuals prescribed antidepressant medication ($\chi^2 = 1.3, p = 0.74$). Thus, the BDI, BDI-II, medication, and SCID-N/P data converge to indicate that PFC lesion laterality has no long-term systematic effect on overall depressive symptomatology.

In the present study, we investigated the effect of PFC lesion laterality on depressive symptomatology in a unique sample of

Table 2

Depression data.

Group	Phase 2 BDI	Phase 3 BDI-II	Antidep. Meds	MDD lifetime diagnosis
Left PFC lesion (<i>n</i> = 21)	9.3 (6.6)	8.4 (8.0)	0.12	0.10
Right PFC lesion (<i>n</i> = 18)	7.2 (5.9)	9.4 (11.4)	0.31	0.17
Non-PFC lesion (<i>n</i> = 38)	10.5 (9.6)	8.9 (7.5)	0.22	0.26
Non-brain-damaged (<i>n</i> = 31)	8.3 (6.7)	12.2 (9.0)	0.30	0.23

For "Phase 2 BDI" and "Phase 3 BDI-II," data are presented as means with standard deviations in parentheses. "Antidep. Meds" refers to the proportion of individuals in each group prescribed antidepressant medication at the time of the Phase 3 evaluation. "MDD Lifetime Diagnosis" refers to the proportion of individuals in each group with any current or previous occurrence of major depressive disorder, based on the SCID-N/P.

brain-injured Vietnam veterans. This study represents a novel contribution to the ongoing investigation of functional PFC asymmetry in depression, as previous lesion studies on this topic have almost exclusively involved stroke patients within two years of lesion onset. The participants in this study have a different lesion etiology (penetrating head injury), multiple long-term evaluations (roughly 15 and 35 years post-injury, respectively) and importantly, an increased susceptibility to affective disorders as a result of emotionally traumatic combat experience [5]. Given these distinct characteristics of the patient sample, this study provides a key test of whether PFC lesion laterality is indeed a critical factor in the long-term severity of depressive symptoms.

Our main finding is that PFC lesion laterality had no significant effect on depression severity at either timepoint (Phase 2 or Phase 3). The relatively low overall BDI scores for the PFC lesion groups (both groups had mean scores less than 10 for both timepoints) suggest that unilateral PFC damage does not confer elevated long-term risk for depression. The lack of an association between unilateral PFC damage and overall depression severity converges with several reviews and meta-analyses of the post-stroke depression literature [4,15,16]. However, it is important to note that previous stroke studies have largely focused on the acute recovery period, whereas our study focuses on chronic, long-term outcomes.

The present results challenge neuropathological models of depression that propose gross hemispheric asymmetry in PFC. Instead, we favor a neuroanatomical model in which the development of depression is tied to the function of distinct subregions within PFC, specifically the ventromedial and dorsolateral sectors. In support of this view, we have found that bilateral lesions to ventromedial PFC confer resistance to depression, whereas bilateral lesions involving dorsolateral PFC confer susceptibility to depression [8]. In the present study, we were unable to contrast the effects unilateral ventromedial and dorsolateral PFC lesions on depression, as the unilateral PFC lesions typically involved both dorsal and ventral areas. Future research on the role of PFC in depression may benefit from a consideration of functional specialization within each hemisphere, as well as functional specialization between hemispheres.

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