Areas of Brain Damage Underlying Increased Reports of Behavioral Disinhibition

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Disinhibition, the inability to inhibit inappropriate behavior, is seen in frontal-temporal degeneration, Alzheimer's disease, and stroke. Behavioral disinhibition leads to social and emotional impairments, including impulsive behavior and disregard for social conventions. The authors investigated the effects of lesions on behavioral disinhibition measured by the Neuropsychiatric Inventory in 177 veterans with traumatic brain injuries. The authors performed voxel-based lesion-symptom mapping using MEDx. Damage in the frontal and temporal lobes, gyrus rectus, and insula was associated with greater behavioral disinhibition, providing further evidence of the frontal lobe's involvement in behavioral inhibition and suggesting that these regions are necessary to inhibit improper behavior.

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Disinhibition, the inability to inhibit inappropriate behavior, involves impulsivity, poor risk assessments, and disregard for social conventions.[1] Disinhibition interferes with the ability to inhibit automatic behaviors, urges, and emotions and impedes goal-directed behavior, such as resisting temptation, delaying gratification, and controlling impulses,[2–4] and therefore can lead to reduced social acceptance. It is not known whether the same mechanisms are responsible for both social inhibition and lower levels of inhibitory control. Dimitrov et al.[5] stated that social inhibition may be at the top of the control versus automatic continuum, whereas inhibition of simple movement may be at the bottom. In this paper, we focused on social inhibition rather than motor responses.

Evidence indicates that the right inferior frontal cortex is important in behavioral inhibition, including cognitive processes, social behavior, and inhibition of motor responses. Damage to the right inferior frontal cortex lowers performance in executive control tasks, most likely by disrupting inhibition.[6] The left prefrontal cortex and anterior cingulate cortex are also involved in inhibition. The left prefrontal cortex may help prepare upcoming behavior, maintain an appropriate task set, and correct behavior following an error.[7,8] The anterior cingulate cortex is involved in conflict detection and evaluative processes indicating when control needs to be more strongly engaged.[8] A voxel-based morphometry study of patients with Alzheimer's disease found that greater behavioral disinhibition, as measured using the Neuropsychiatric Inventory (NPI),[9] a structured, caregiver-based interview, was strongly associated with reduced gray matter volume in the right middle frontal and precentral gyri and bilateral cingulate.[10]

We used the NPI to record observations of behavioral disinhibition in a large sample of patients with penetrating traumatic brain injury (pTBI). As lesion studies provide complementary information to neuroimaging studies, we performed a whole-brain voxel-based lesion-symptom mapping analysis (examining voxel-by-voxel the relationship between NPI disinhibition scores and lesion locations) to investigate the brain regions responsible for behavioral inhibition. We predicted that areas in the brain associated with this measure would include frontal regions in the right hemisphere, the anterior cingulate cortex, and precentral gyri.

METHODS

Subjects

Participants were 177 male veterans who received TBIs while serving in the Vietnam War between 1967 and 1970.[11] They were drawn from phase III (2003–2006) of the W.F. Caveness Vietnam Head Injury Study registry[11] conducted at the National Naval Medical Center in Bethesda, MD, 33–39 years after injury. Most of the injuries resulted from low-velocity penetrating fragments (missile fragments or gunshots). All veterans with TBI for whom we had NPI and CT data were included. The veteran cohort offered a number of methodological advantages including its large sample size, demographic uniformity, and access to preinjury data to compare with postinjury performance. All study procedures were approved by the Institutional Review Board of the National Naval Medical Center. All subjects gave written

informed consent in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Procedure

Neuropsychological functions, including intelligence, emotional intelligence, empathy, and depression, were assessed in a battery of tests administered over 5–7 days. The NPI was part of this testing, which was designed to determine the degree of reported psychopathology in patients with brain disorders.[9] It assesses behavioral disturbances/neuropsychiatric symptoms in 10 areas: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behavior. The questions pertain to changes in the patient's behavior since the onset of the illness or injury. The examiner read the questions to a caregiver familiar with the patient's behavior. Caregivers were generally spouses, partners, or adult children; they rated the participant's symptom frequency and severity. Frequency scores range from 1 to 4 (where 1 = occasionally, less than once per week; 2 = often, about once per week; 3 = frequently, several times per week but less than every day; 4 = very frequently, once or more per day or continuously). Severity scores range from 1 to 3 (where 1 = mild, 2 = moderate, 3 = marked). Each symptom's score is the product of the frequency times the severity for that particular behavior, with a maximum score of 12. We used the scores of the disinhibition item, which asks "Does the patient seem to act impulsively without thinking? Does he do or say things that are not usually done or said in public? Does he do things that are embarrassing to you or others?" Caregivers were asked to provide the information because patients may distort or not be fully aware of their behavior, may not behave abnormally in the presence of the clinician, and may not be able to grasp scaling concepts necessary for determining severity and frequency.[9,12]

In addition, we used pre- and postinjury general intelligence scores from the Armed Forces Qualification Test (AFQT-7A, U.S. Department of Defense, 1960). Scores on this test correlate highly with the WAIS.[13,14] We measured emotional intelligence with the Strategic Emotional Intelligence items on the Mayer-Salovey-Caruso Emotional Intelligence Test.[15] We measured emotional empathy with the Balanced Emotional Empathy Scale.[16] Finally, we measured lifetime prevalence of depression using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/NP).[17]

CT and Lesion Identification

Because many of the pTBI veterans had intracranial metal fragments, CT scans rather than MRIs were performed. Axial CT scans were acquired without contrast on a GE LightSpeed Plus CT scanner at the Bethesda Naval Hospital. Images were reconstructed with an in-plane voxel size of 0.4×0.4 mm, an overlapping slice thickness of 2.5 mm, and a 1-mm slice interval. Lesion volume was calculated by summing the traced areas and multiplying by slice thickness.

Lesion location was determined by manual tracing on each slice using the "Analysis of Brain Lesion" (ABLe) software[18] implemented in MEDx v3.44. Similar to the methodology used in many other lesion analysis studies,[19–26] the lesion tracing was performed manually on each slice in native space by a neuropsychiatrist with clinical experience in reading CT scans (VR) and reviewed by the principle investigator who was blind to the results of the clinical evaluation and neuropsychological testing (JG), enabling a reliable consensus regarding lesion boundaries. These boundaries were determined by judging the demarcation made between the hypointensity of the lesions and the normal brain. Scans were registered to a template in Montreal Neurological Institute space, using the AIR algorithm with a 12-parameter affine fit.[27] Voxels inside the traced lesion were excluded from the registration. Registration accuracy was verified using MEDx ABLe.

Statistical Analysis

Behavioral Analysis. We computed means and standard deviations for demographic information and neurobehavioral scores using IBM SPSS 20 (www.spss.com). We also performed two-tailed Spearman's correlations on NPI disinhibition scores with pre- and postinjury IQ, Mayer-Salovey-Caruso Emotional Intelligence Test, Balanced Emotional Empathy Scale, and depression. An α level of 0.05 was used.

Lesion Analysis. We created a lesion density map to show the number of veterans with pTBI who had damage at each voxel by overlaying their individual normalized lesion maps. Next, we used the NPI disinhibition scores and normalized lesion images to perform voxel-based lesion-symptom mapping using the toolbox in MEDx. At each voxel, behavioral scores were compared for those patients who had a lesion at that voxel versus those who did not, producing a *t*-statistic for each voxel. We used a one-tailed t test with a false discovery rate correction (q of 0.05) for multiple comparisons[28] and a minimum cluster size of 10 voxels, and we limited the analysis to voxels damaged in at least four veterans.[29] Gray matter location was obtained from the Automated Anatomical Labeling atlas.[30] To investigate the potential effect of brain volume loss, we performed independent sample t tests on percentages of loss between the resulting lesion groups.

RESULTS

Behavioral Results

Nineteen percent of the patients with pTBIs were rated by their caregiver as exhibiting behavioral disinhibition. Table 1 displays the means of the demographic information and neurobehavioral scores.

A significant negative correlation was found between disinhibition and postinjury Armed Forces Qualification Test scores (r_s=−0.23, p=0.003), meaning that disinhibition was associated with lower postinjury intelligence scores. To rule out the possibility that this association reflected a preinjury tendency toward disinhibition, we performed a Spearman's

TABLE 1. Means ± Standard Deviations for Demographic Information and Neurobehavioral Measures[a]

Characteristic	pTBI (N=177)
Age (years)	58.44±3.13
Education (years)	14.84±2.55
Preinjury AFQT percentile	61.45±25.48
Postinjury (phase III) AFQT percentile	53.27±24.71
MSCEIT strategic emotional intelligence	88.80±12.00
BEES total Z scores	0.72±1.08
SCID-I/NP lifetime prevalence of major depression	1.41±0.79
NPI disinhibition frequency x severity	0.54±1.39

[a] AFQT, Armed Forces Qualification Test; BEES, Balanced Emotional Empathy Scale; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test; NPI, Neuropsychiatric Inventory; pTBI, penetrating traumatic brain injury; SCID-I/NP, Structured Clinical Interview for DSM-IV Axis I Disorders (nonpatient version).

correlation between disinhibition and preinjury Armed Forces Qualification Test and found no significant correlation (r_s=−0.08, p=0.28). A marginal correlation was identified between disinhibition and depression (r_s=0.15, p=0.056), but no significant correlation was found between disinhibition and Mayer-Salovey-Caruso Emotional Intelligence Test scores (r_s=−0.12, p=0.14) or between disinhibition and Balanced Emotional Empathy Scale scores (r_s=0.06, p=0.42).

Voxel-Based Lesion-Symptom Mapping Results

The lesion density map is shown in Figure 1. The maximum overlap occurred in the prefrontal areas in 28 veterans.

The voxel-based lesion-symptom mapping analysis revealed an association between disinhibition and lesioned voxels in the following regions: mainly right orbitofrontal cortex, bilateral insula, right temporal lobe, left frontal, precentral and postcentral regions, and bilateral gyrus rectus (Figure 2; Table 2). High t scores (warm colors) indicate that lesions in these areas had a highly significant effect on disinhibition.

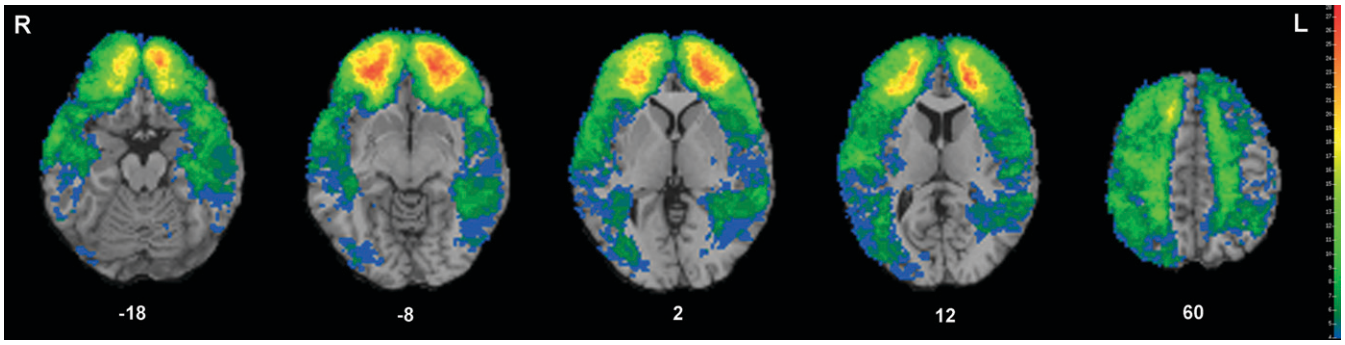
To investigate whether the voxel-based lesion-symptom mapping results could be partially caused by differences in brain volume loss, we performed independent t tests comparing percentages of loss between the two resulting lesion groups. Veterans with damage in lesion areas significant for disinhibition (N=95) had a significantly greater percentage of volume loss than those with damage only in other areas [N=82; 4.3±4.2% versus 1.5±1.3%; $t(116)$ = 6.09, p<0.001]. To investigate the potential impact of this, we performed a Spearman's correlation between percentage of brain volume loss and disinhibition in all veterans with pTBIs and found a marginally significant correlation (r_s=0.14, p=0.06).

DISCUSSION

We used a whole brain approach to investigate specific brain regions responsible for behavioral disinhibition in a large sample of patients with pTBIs. Nineteen percent of our patients with pTBIs were rated by their caregiver as exhibiting behavioral disinhibition. This rate is similar to that for patients with Alzheimer's disease,[10,31] lower than the rate for a younger group of patients with severe diffuse axonal or focal TBI,[32] and higher than the rate for patients with Parkinson's disease[33] or corticobasal degeneration.[34]

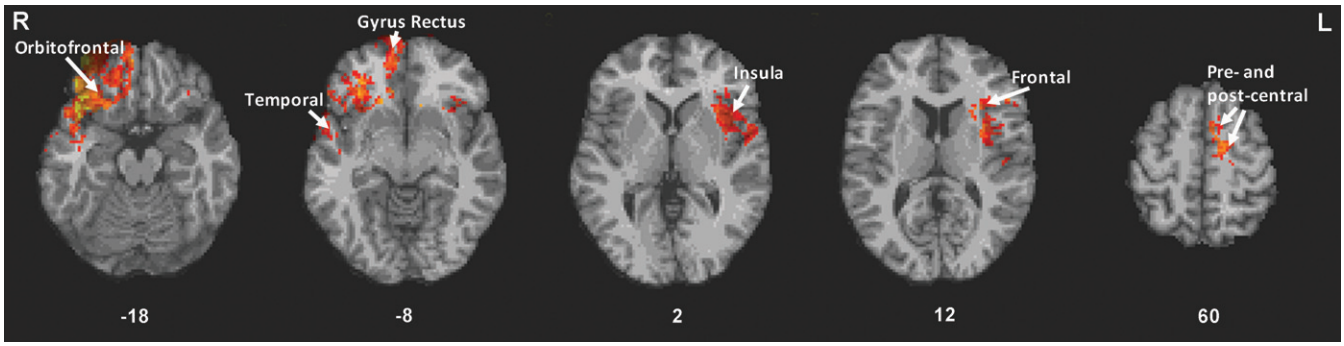
Our voxel-based lesion-symptom mapping analysis revealed an association between greater behavioral disinhibition and the following regions: mainly right orbitofrontal regions, bilateral insula, right temporal lobe, left frontal, precentral and postcentral regions, and bilateral gyrus rectus. Other patient studies showed similar findings. For example, patients with ventral frontal lesions had greater disinhibition than patients with nonventral frontal lesions.[35] In patients with frontotemporal dementia, a positive correlation between NPI disinhibition and glucose hypometabolism in the bilateral ventromedial orbitofrontal cortex/gyrus rectus, was found.[36] Similarly, in individuals with mild cognitive impairment or dementia, a positive association between NPI disinhibition and bilateral orbitofrontal cortex atrophy was revealed.[37] In a voxel-based morphometry study of patients with frontotemporal dementia, NPI disinhibition was associated with atrophy in regions similar to those we found, including the bilateral orbitofrontal cortex, bilateral inferior frontal cortex, bilateral insula, and right middle temporal regions.[38] Another study of patients with behavioral variant frontotemporal dementia and Alzheimer's disease found that NPI disinhibition

FIGURE 1. Lesion Density Map[a]



[a] Axial slices. Color indicates the number of lesions overlapping at each voxel, where warmer colors indicate more veterans had lesions at those locations. The greatest overlap was found in the prefrontal regions, with 28 veterans having lesions in these areas (shown in red). Slice numbers are displayed below each slice. The left is on the viewer's right.

FIGURE 2. Voxel-Based Lesion-Symptom Map for Disinhibition[a]



[a] Axial slices. Color indicates brain regions with a significant association between lesion location and Neuropsychiatric Inventory disinhibition [one-tailed t test, *q*(false discovery rate) = 0.05, minimum cluster size = 10 voxels], with yellow indicating the highest association. The voxel-based lesion-symptom mapping analysis was limited to those voxels where at least four veterans had damage. Slice numbers are displayed below each slice. The left is on the viewer's right.

was associated with atrophy in the bilateral orbitofrontal cortex and left temporal pole.[39] The same study found that atrophy in the bilateral orbitofrontal cortex, subgenual areas, medial prefrontal cortex, and temporal pole covaried with errors in inhibiting prepotent verbal responses.

Our results are consistent with the involvement of the right orbitofrontal cortex and inferior frontal cortex in disinhibition, as demonstrated by the above studies, and support this area's importance in self-control[3] and response stopping.[40] They add to evidence that the ventral frontal cortex is crucial not only in motor response inhibition but also in the control of social behavior. Dillon and Pizzagalli[41] suggested that the right ventrolateral prefrontal cortex may support a general inhibitory process. In addition to the right orbitofrontal cortex/inferior frontal cortex, we found frontal regions in the left hemisphere, including inferior, middle, and superior frontal areas, that when damaged were associated with increased disinhibition. This is consistent with the left inferior, middle, and superior frontal cortex activation found in the incongruent versus neutral condition in a Flanker task,[42] although those authors also found similar regions on the right. Aron et al.[6] suggested a functional division in inhibition where the left prefrontal cortex's role is maintaining goals/sets, the anterior cingulate cortex's is to detect conflict when the current condition does not match those goals, and the right inferior frontal cortex's is to suppress irrelevant responses.

The bilateral gyrus rectus involvement that we found is consistent with a study showing that patients with gyrus rectus lesions performed poorly on the Trail Making B test, which is considered an inhibition task.[43]

In addition to frontal areas, we found lesioned areas in the bilateral insula associated with disinhibition. Insula activation has been found during a Flanker task[42] and a response inhibition task.[7] The insular cortex has been implicated in task-set maintenance and top-down control.[44] We also found that damage to the right temporal lobe, including the pole, was associated with disinhibition. Consistent with this, patients with temporal variant frontotemporal dementia with atrophy in either temporal lobe exhibited disinhibition.[45] In addition, disinhibition, as measured by the Frontal Systems Behavior Scale, was associated with gray matter loss in the right medial and superior temporal lobe in patients with frontotemporal dementia.[46] The temporal lobe is also involved in inhibiting prepotent verbal responses.[39]

Motor inhibition tasks often activate parietal areas, but we did not find an association between parietal damage and disinhibition. We had fewer patients with damage to parietal regions and therefore had less power to detect an association there; however,

TABLE 2. Voxel-Based Lesion-Symptom Mapping Results[a]

Location	*x*	*y*	*z*	Volume (Voxels)	Hemisphere	Z
Inferior, middle, and superior orbitofrontal; middle and superior temporal and temporal pole; gyrus rectus; insula	42	16	−18	3278	R	6.90
Insula; inferior, middle, and superior frontal; inferior triangular frontal; supplementary motor area; Rolandic operculum; precentral	−20	12	28	4663	L	6.26
Middle and inferior temporal lobe, including temporal pole	58	2	−20	182	R	3.94
Gyrus rectus; caudate; superior orbitofrontal	−12	22	−10	22	L	4.79
Inferior frontal operculum; precentral	−58	12	26	15	L	4.00
Postcentral; precentral	−34	−28	50	22	L	3.62
Precentral	−32	−14	56	12	L	3.62
Middle frontal	−36	14	54	11	L	2.71

[a] AAL labels of damaged brain regions associated with greater NPI disinhibition. *x, y, z* = Talairach coordinates. L: left; R: right.

inferior parietal lobe activation during response inhibition has been shown to be stronger in women,[47] whereas our sample included only men. In addition, no impairment was found in Stop-Signal task performance during disruptive transcranial magnetic stimulation over the right parietal region,[48] suggesting that it may not be crucial for inhibition. Alternatively, long-range connectivity between the frontal and parietal regions may have been disrupted in our patients with TBI, degrading the ability of parietal regions to inhibit behavior.

The strengths of our study include our whole brain analysis that was not restricted to a priori regions of interest, our large sample size, our patients with focal, rather than diffuse, lesions, and our homogeneous study population; however, this homogeneity (using only older men) makes the generalizability of the results to other populations uncertain. In addition, CT scans have less detail than MRIs, and the AIR registration process used in ABLe is a 12-parameter linear fit, which can lead to imperfect registration. In addition, pTBI can create positional shifts in brain tissue, as well as more chronic changes due to contraction in glial scars or the osmotic enlargement of fluid-filled spaces.

In conclusion, to our knowledge, this is the largest study of the neural correlates of behavioral disinhibition associated with focal brain lesions. Disinhibition is a debilitating problem leading to impulsive and socially inappropriate behavior. The identification of relationships between behavioral disinhibition and lesion location can help clinicians predict behavioral risk and develop coping strategies for patients and caregivers. On the positive side, the majority of veterans with pTBIs did not exhibit disinhibited behaviors. It is important to note that we have taken a snapshot in time and do not know whether they were disinhibited for a while after their injury but have since recovered.

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