Archival Report

Biological Psychiatry: CNNI

Frontolimbic Morphometric Abnormalities in Intermittent Explosive Disorder and Aggression

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ABSTRACT

BACKGROUND: Converging evidence from neuroimaging studies suggests that impulsive aggression, the core behavior in the DSM-5 diagnosis intermittent explosive disorder (IED), is regulated by frontolimbic brain structures, particularly orbitofrontal cortex, ventral medial prefrontal cortex, anterior cingulate cortex, amygdala, insula, and uncus. Despite this evidence, no brain volumetric studies of IED have been reported as yet. This study was conducted to test the hypothesis that gray matter volume in frontolimbic brain structures of subjects with IED is lower than in healthy subjects and subjects with other psychiatric conditions.

METHODS: High-resolution magnetic resonance imaging scans using a three-dimensional magnetization-prepared rapid acquisition gradient-echo sequence were performed in 168 subjects ($n = 53$ healthy control subjects, $n = 58$ psychiatric controls, $n = 57$ subjects with IED). Imaging data were analyzed by voxel-based morphometry methods employing Statistical Parametric Mapping (SPM8) software.

RESULTS: Gray matter volume was found to be significantly lower in subjects with IED compared with healthy control subjects and psychiatric controls in orbitofrontal cortex, ventral medial prefrontal cortex, anterior cingulate cortex, amygdala, insula, and uncus. These differences were not due to various confounding factors or to comorbidity with other disorders previously reported to have reduced gray matter volume. Gray matter volume in these areas was significantly and inversely correlated with measures of aggression.

CONCLUSIONS: Reductions in the gray matter volume of frontolimbic structures may be a neuronal characteristic of impulsively aggressive individuals with DSM-5 IED. These data suggest an anatomic correlate accounting for functional deficits in social-emotional information processing in these individuals.

Keywords: Aggression, Amygdala, Anterior cingulate cortex, Insula, Intermittent explosive disorder, Medial prefrontal cortex, Orbitofrontal cortex, Uncus, Voxel-based morphometry

http://dx.doi.org/10.1016/j.bpsc.2015.09.006

Converging evidence from studies of human lesions and from functional and structural neuroimaging studies suggest that impulsive aggressive behavior is regulated by frontolimbic regions in the brain, particularly orbitofrontal cortex (OFC), ventral medial prefrontal cortex (mPFC), amygdala, and hippocampus, among other brain regions. However, most studies to date have examined a variety of subjects with different disorders or conditions that may have more than less premeditated aggression or levels of aggression that are of only mild to moderate severity (1). For example, structural neuroimaging studies of such "aggressive" individuals (i.e., individuals with borderline personality disorder, antisocial personality disorder, or psychopathic personality) reported variable reductions in gray matter volume in these frontolimbic regions (2–8).

To study impulsive aggression in its purest culture, we investigated the clinical neuroscience of intermittent explosive disorder (IED) as defined by DSM-5. The behavioral disorder IED describes individuals with recurrent, problematic, impulsive aggression (1) and has a lifetime prevalence, by DSM-IV criteria, of at least 4% (9). The disorder runs in families (10), and the core behaviors of IED are under genetic influence (11). It is also associated with reduced serotonin function (12), and the impulsive aggressive behavior of individuals with IED responds to treatment with serotonin uptake inhibitors (13).

We sought to test the hypothesis that individuals with substantial histories of impulsive aggressive behavior have abnormalities in frontolimbic regions and circuits. We conducted a voxel-based morphometry (VBM) study in subjects with IED as defined by DSM-5 and in nonaggressive healthy control (HC) subjects and subjects with other psychiatric conditions (psychiatric control [PC] subjects). Follow-up analyses were performed to determine if results were influenced by clinical characteristics, comorbidity with other disorders, state depression and anxiety, history of psychotropic medication exposure, and history of mild to moderate head injury.

METHODS AND MATERIALS

Subjects

High-resolution structural magnetic resonance imaging was performed in 168 right handed, medication-free, physically healthy individuals. Subjects were recruited through public service announcements and advertisements in newspapers

 ISSN: 2451-9022

Table 1. Syndromal and Personality Disorder Diagnoses in Psychiatric Control and Intermittent Explosive Disorder Subjects

	PC (n = 58)	IED (n = 57)	p
Current Syndromal Disorders			
Any depressive or anxiety disorder	33 (56.9%)	24 (42.1%)	.137
Any depressive disorder	2 (3.4%)	14 (24.6%)	.001[a]
Any anxiety disorder	33 (56.9%)	18 (31.6%)	.009
Any substance use disorder	0 (0%)	0 (0%)	.999
Any stress and trauma disorder	2 (3.4%)	11 (19.3%)	< .008
Any eating disorder	2 (3.4%)	3 (5.3%)	.679
Any obsessive-compulsive disorder	0 (0%)	1 (1.8%)	.496
Any somatoform disorder	2 (3.4%)	1 (1.8%)	.999
Non-IED impulse control disorder	0 (0%)	1 (1.8%)	.496
Lifetime Syndromal Disorders			
Any depressive or anxiety disorder	41 (70.7%)	41 (71.9%)	.999
Any depressive disorder	21 (36.2%)	33 (68.4%)	.001[a]
Any anxiety disorder	37 (63.8%)	19 (33.3%)	.001[a]
Any substance use disorder	23 (39.7%)	26 (45.6%)	.263
Any stress and trauma disorder	10 (17.2%)	13 (22.9%)	.492
Any eating disorder	3 (5.2%)	4 (7.0%)	.717
Any obsessive-compulsive disorder	0 (0%)	2 (3.5%)	.243
Any somatoform disorder	0 (0%)	1 (1.8%)	.999
Non-IED impulse control disorder	1 (1.7%)	2 (3.5%)	.618
Personality Disorders			
Any personality disorder	37 (63.8%)	54 (94.7%)	< .001[a]
Personality disorder clusters			
Cluster A (odd)	2 (3.4%)	10 (17.5%)	.001[a]
Cluster B (dramatic)	2 (3.4%)	24 (42.1%)	< .001[a]
Cluster C (anxious)	29 (50.0%)	18 (31.6%)	.058
PD-NOS	7 (12.1%)	19 (33.3%)	.008
Specific personality disorders			
Borderline personality disorder	2 (3.4%)	25 (43.9%)	< .001[a]
Antisocial personality disorder	0 (0%)	10 (17.5%)	.001[a]
PCL-SV psychopathic personality	0 (0%)	10 (17.5%)	.001[a]

IED, intermittent explosive disorder; PC, psychiatric control; PCL-SV, Psychopathy Checklist: Screening Version; PD-NOS, personality disorder, not otherwise specified.

[a]$p < .05$ after correcting for multiple comparisons.

and other media seeking out individuals who 1) reported psychosocial difficulty related to a psychiatric (but nonbipolar/nonpsychotic) condition (PC subjects) or who 2) had little evidence of psychopathology (HC subjects). All subjects gave informed consent and signed the informed consent document approved by our institutional review board. After a detailed diagnostic assessment (Supplement 1), 57 subjects met DSM-5 criteria for IED and 58 subjects met criteria for other DSM-5 diagnoses (Table 1). Of these subjects, most (78.3%) reported a lifetime history of formal psychiatric evaluation or treatment or both, and nearly one-third (28.7%) reported lifetime exposure to psychotropic medication. However, all subjects were at least 4 weeks free of all medication, and most were medication free for much longer.

Assessment of Aggression, Impulsivity, Suicidal Behavior, and Related Variables

Aggression was assessed using the Aggression score from the Life History of Aggression (14) interview and the Aggression (Physical, Verbal, and Anger) score from the Buss-Perry Aggression questionnaire (15). The Life History of Aggression interview assesses history of actual aggressive behavior, and the Buss-Perry Aggression questionnaire assesses aggressive tendencies as a personality trait. Impulsivity was assessed using the Life History of Impulsive Behavior (16) and the Barratt Impulsiveness Scale Version 11 (17). The Life History of Impulsive Behavior assesses history of actual impulsive behavior, and the Barratt Impulsiveness Scale assesses impulsive tendencies as a personality trait. Life history of suicidal and self-injurious behavior was assessed during the diagnostic assessment. The Psychopathy Checklist: Screening Version (18) was used to assess for the presence of psychopathic personality. History of childhood trauma and maltreatment was assessed using the Childhood Trauma Questionnaire (19). Racial data reflected self-identified racial characteristics of subjects. Details on assessments for state depression, state anxiety, and history of head injury/loss of consciousness are in Supplement 1.