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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

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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

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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.

Image Acquisition

Imaging data were acquired with a 3-tesla SIGNA magnetic resonance imaging system (GE Healthcare, Waukesha, Wisconsin) using three-dimensional magnetization-prepared rapid acquisition gradient-echo sequence. Anatomic images were obtained using a sagittal three-dimensional gradient echo T1-weighted sequence (repetition time = 8 ms, echo time = 3.2 ms, inversion time = 725 ms, flip angle = 6°, field of view = 240 mm × 240 mm, slice thickness = 1.5 mm, 120 slices, 256 × 256 matrix).

Image Processing and Analysis

The VBM procedures used VBM toolbox developed by Christian Gaser (http://dbm.neuro.uni-jena.de/vbm) for SPM8 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, University College, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm). Each image was first aligned along the anterior-posterior commissure line to provide a uniform and optimal starting position for subsequent analyses. Images were segmented into gray matter, white matter, and cerebrospinal fluid by applying the default SPM8 tissue probability map and spatially normalized with high-dimensional DARTEL toolbox normalization according to the unified segmentation model (20). Segmented images were resampled to 1.5 mm^3 resolution. Voxel values from gray matter and white matter images were subsequently multiplied by Jacobian determinants of the normalization matrix to permit for detection of true volumetric differences accounting for global and regional differences in the absolute volume of gray matter (21). Data quality was ensured by visually examining native volumes for artifacts and proper orientation and assessing sample homogeneity along the Montreal Neurological Institute template origin with proportional scaling via boxplot and covariance matrices. The final images were smoothed by applying a Gaussian kernel of full width at half maximum of 10 mm, creating a local weighted average of surrounding pixels.

The VBM group differences were evaluated using the smoothed, modulated, warped segments in a full factorial analysis of covariance (ANCOVA) model with diagnostic group as factor and age, sex, and total intracranial volume as covariates. The variables in the general linear model were fitted to a linear equation using the "Estimate" function in SPM. To test group differences, voxel-by-voxel Student *t* tests were computed across the whole brain with a masked threshold set to absolute at .2 to determine global differences in gray matter volumes based on diagnosis, contrasting IED subjects versus PC subjects versus HC subjects. Whole-brain cluster-based significance thresholding was determined via simulation using the ClusterSim utility (10,000 iterations; http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html). Given smoothness estimates of the data (4.6 mm × 5.3 mm × 5.0 mm) across our entire gray matter mask, normalized to Montreal Neurological Institute space with a volume of 1064 cm^3, family-wise error correction at $\alpha < .05$ is realized with a voxel threshold of $p < .005$ with minimum cluster size of 104 voxels (351 mm^3).

Statistical Analysis

The primary analysis on whole-brain data revealed significantly reduced gray matter volumes in IED subjects compared with HC subjects and PC subjects in six frontolimbic areas: OFC, mPFC, anterior cingulate cortex (ACC), right amygdala, left insula, and left uncus. Because multiple regression analysis revealed that no one region uniquely accounted for variance in these aggression scores, a composite measure of the extracted frontolimbic gray matter volume (FL-GMV; arbitrary units) from these areas was created by taking the mean of the *Z*-scores of individual gray matter volumes in a data reduction step to minimize the number of comparisons and correlations. Aggression and impulsivity were also analyzed as composite measures of their source data (aggression, Life History of Aggression/Buss-Perry Aggression; impulsivity, Life History of Impulsive Behavior/Barratt Impulsiveness Scale) as previously described (12). Subsequent analyses involved multivariate analysis of covariance, ANCOVA, and multiple regression with a two-tailed α level of .05.

RESULTS

Characteristics of the Sample

Although modest-sized differences in demographic variables were noted among HC subjects, PC subjects, and IED subjects (Table 2), multiple regression analysis revealed that only age, sex, race, and education were uniquely related to VBM variables. These four variables were used as covariates in subsequent analyses. For behavioral variables, PC subjects and IED subjects differed from HC subjects as expected (Table 2). Diagnostically, PC subjects and IED subjects had similar frequencies of current/lifetime mood and anxiety disorders, whereas IED subjects had higher frequencies of selected personality disorders (Table 1).

Group Comparisons of Voxelwise Whole-Brain Data

All clusters showing between-group differences with gray matter volume ≥104 voxels are listed in Table 3 and illustrated in Figure 1A. Compared with HC subjects and PC subjects, IED subjects displayed a reduction in gray matter volume in OFC, mPFC, ACC, right amygdala, left insula, and left uncus. No brain region displayed greater gray matter volume values for IED subjects compared with HC subjects or PC subjects. Finally, neither total intracranial volume (IED subjects 1372.8 ± 161.8 vs. PC subjects 1373.0 ± 122.4 vs. HC subjects 1394.3 ± 141.0; $F_{2,161} = .80$, $p = .450$) nor white matter volume (IED subjects 519.7 ± 82.3 vs. PC subjects 521.4 ± 51.0 vs. HC subjects 531.8 ± 69.0; $F_{2,161} = .95$, $p = .391$) differed in IED subjects compared with HC subjects and PC subjects.

Group Comparisons of Extracted Raw and Composite FL-GMV Values

The multivariate analysis of covariance (age, sex, race, and education as covariates) of extracted raw FL-GMV values revealed significant reductions in each frontolimbic area (Wilks $\lambda = .83$, $F_{12,312} = 2.57$, $p = .003$), with percent reductions from HC subjects ranging from 5.1% (ACC) to 11.% (left uncus; mean ± SD, 7.8% ± 2.3%) and percent reductions from PC subjects ranging from 4.8% (right amygdala) to 9.3% (left uncus; mean ± SD, 7.0% ± 1.4%) (Figure 1B). The ANCOVA of composite FL-GMV values revealed the same

Table 2. Demographic and Psychometric Characteristics of Subjects

	HC (n = 53)	PC (n = 58)	IED (n = 57)	p
Demographic Variables				
Age (years)	31.2 ± 7.5	30.8 ± 9.0	34.4 ± 8.6	.047[a]
Sex (% male)	47	48	53	.830[b]
Race (% W/AA/other)	74/11/15	76/14/10	42/26/32	.004[b]
SES score	47.5 ± 10.7	47.8 ± 11.9	39.3 ± 12.3	< .001[a]
Education (years)	16.2 ± 2.0	16.2 ± 2.5	14.8 ± 2.0	< .001[a]
Psychometric Variables				
LHA aggression	5.5 ± 2.9	7.3 ± 5.5	18.0 ± 4.6	< .001[a]
BPA aggression	14.7 ± 5.0	15.5 ± 4.4	24.7 ± 5.5	< .001[a]
LHIB impulsivity	31.2 ± 20.5	46.5 ± 21.5	50.5 ± 17.8	< .001[a]
BIS-11 impulsivity	55.9 ± 8.8	61.0 ± 10.0	69.2 ± 11.1	< .001[a]
BDI state depression	2.8 ± 8.1	9.3 ± 8.3	17.8 ± 13.2	< .001[a]
BDI state anxiety	23.0 ± 7.9	29.7 ± 8.0	31.6 ± 7.9	< .001[a]
CTQ score	32.4 ± 7.6	37.5 ± 12.5	55.5 ± 17.9	< .001[a]
Self-Directed Aggression Variables				
Suicide attempt (%)	0 (0%)	3 (5.2%)	10 (17.5%)	< .000[b]
Self-injurious behavior (%)	0 (0%)	3 (5.2%)	4 (7.0%)	= .164[b]

AA, African American; BDI, Beck Depression Inventory; BIS-11, Barratt Impulsiveness Scale Version 11; BPA, Buss-Perry Aggression; CTQ, Child Trauma Questionnaire; HC, healthy control; IED, intermittent explosive disorder; LHA, Life History of Aggression; LHIB, Life History of Impulsive Behavior; PC, psychiatric control; SES, socioeconomic status; W, white.

[a]Student t test.

[b]χ^2 test.

result ($F_{1,161}$ = 9.83, p < .001; IED subjects = −.35, 95% confidence interval [CI] −.54 to −.17; PC subjects = .16, 95% CI −.19 to .33; HC subjects = .21, 95% CI .03 to .39).

Composite FL-GMV Values as a Function of History of Suicide Attempt and Self-Injurious Behavior

The ANCOVA revealed no significant influence of suicide attempt ($F_{1,161}$ = 1.84, p = .181) or self-injurious behavior status ($F_{1,161}$ = .89, p = .346) on mean composite FL-GMV values.

Composite FL-GMV Values and Aggression and Impulsivity Scores

Partial correlation with age, sex, race, and education as covariates revealed a significant correlation between composite FL-GMV values and composite aggression scores (partial r = −.24, p = .002) (Figure 2) but not with composite impulsivity scores (partial r = .01, p = .896). Stepwise multiple regression analysis with composite FL-GMV values as dependent variable and covariates (age/sex/race/education) entered at step 1, composite aggression scores entered at

Table 3. Brain Regions Showing Lower Gray Matter Volume in Intermittent Explosive Disorder Subjects Compared With Healthy Control and Psychiatric Control Subjects in Whole-Brain Voxel-Based Morphometry Analysis (IED < PC = HC)

	MNI Coordinates				
Region	x	y	z	Volume (mm^3)	Z Score
Inferior Temporal/Fusiform Gyrus	−45	−19	−36	3537	4.73
Orbitofrontal Gyrus (OFC)	−2	44	−29	17,537	4.42
Medial Frontal Gyrus (mPFC)	3	56	−5	NA	3.81
Anterior Cingulate (ACC)	−5	56	18	NA	3.79
Parahippocampal Gyrus	21	−19	−29	4087	4.32
Amygdala (R-AMYG)	32	2	−26	NA	3.85
Insula (L-INS)/Inferior Frontal Gyrus	−44	12	4	6413	3.90
Superior Temporal Gyrus	−56	−45	25	7094	3.89
Parahippocampal Gyrus/Uncus (L-UNC)	−21	2	−38	2730	3.76
Cerebellum	44	−69	−41	506	3.33
Insula/Inferior Frontal Gyrus	38	16	−3	1222	3.29
Inferior Temporal Gyrus	42	−6	−38	1316	3.26
Superior Temporal Gyrus	−48	−15	0	692	3.14

ACC, anterior cingulate cortex; L-INS, left insula; L-UNC, left uncus; MNI, Montreal Neurological Institute; mPFC, medial prefrontal cortex; NA, not applicable; OFC, orbitofrontal cortex; R-AMYG, right amygdala.

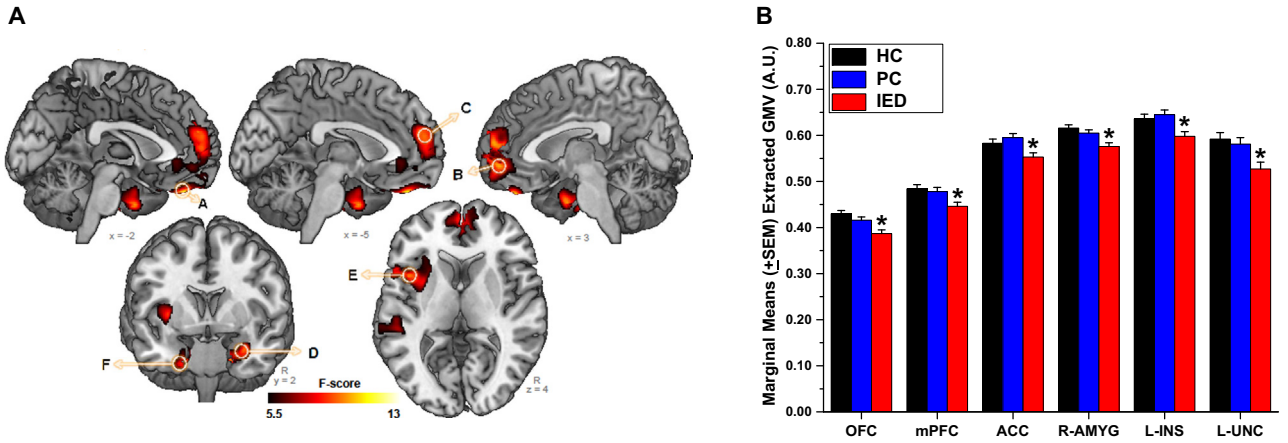

Figure 1. **(A)** Gray matter volume (GMV) comparison of HC vs. PC vs. IED subjects. Reductions in gray matter brain volume in IED subjects in six frontolimbic areas: A, OFC; B, mPFC; C, ACC; D, R-AMYG; E, L-INS; F, L-UNC. Results are displayed on a normalized high-resolution T1 image (statistical maps thresholded at voxel $p < .005$ with cluster size >104 contiguous voxels). **(B)** Gray matter volume (A.U.) extracted from OFC, mPFC, ACC, R-AMYG, L-INS, and L-UNC in HC, PC, and IED subjects. *$p < .001$. ACC, anterior cingulate cortex; A.U., arbitrary units; HC, healthy control; IED, intermittent explosive disorder; L-INS, left insula; L-UNC, left uncus; mPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; PC, psychiatric control; R-AMYG, right amygdala.

step 2, and IED status (IED vs. no IED) entered at step 3 revealed a significant relationship between composite FL-GMV values and composite aggression scores at step 2 (R^2 change = .044, β = −.23, p = .002) but not at step 3 (β = .01, p = .912) after the addition of IED status (R^2 change = .038, β = −.34, p = .003).

Composite FL-GMV Values as a Function of Other Diagnoses

We next explored the effect of four sets of comorbid diagnostic conditions that could influence composite FL-GMV values. These ANCOVA analyses included IED as a separate factor along with the presence or absence of comorbid conditions in question. In each comparison, IED was associated with a significant reduction in composite FL-GMV values ($p < .001$) without effect of comorbid conditions on composite FL-GMV values: 1) current mood ($F_{1,160}$ = 1.01, p = .316), anxiety ($F_{1,160}$ = 2.91, p = .090), or stressor ($F_{1,160}$ = .03, p = .862) disorders; 2) past mood ($F_{1,159}$ = 2.26, p = .134), anxiety ($F_{1,159}$ = .27, p = .601), substance use ($F_{1,159}$ = 1.22, p = .271), or stressor ($F_{1,159}$ = .75, p = .389) disorders; 3) cluster A ($F_{1,160}$ = .00, p = .975), cluster B ($F_{1,160}$ = .83, p = .383), or cluster C ($F_{1,160}$ = .00, p = .954) personality disorders; 4) borderline or antisocial personality disorder ($F_{1,161}$ = .50, p = .482) or psychopathic personality ($F_{1,161}$ = .87, p = .354).

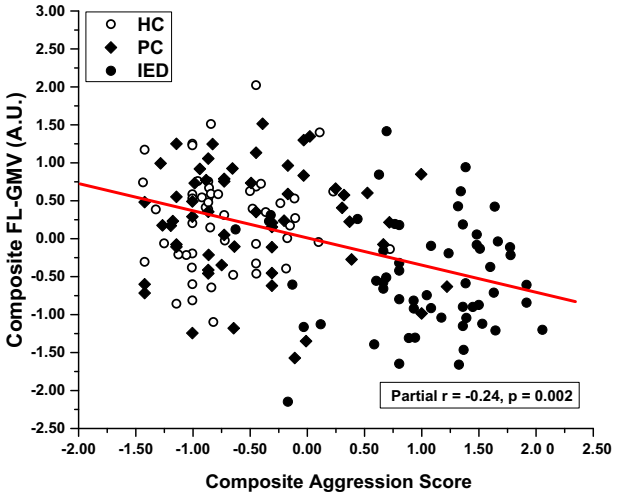

Figure 2. Scatterplot for composite FL-GMV values and composite aggression scores in all subjects (see text). A.U., arbitrary units; FL-GMV, extracted frontolimbic gray matter volume; HC, healthy control; IED, intermittent explosive disorder; PC, psychiatric control.

Relationship Between Composite FL-GMV Values, Other Clinical Variables, and History of Childhood Trauma or Maltreatment

Composite FL-GMV values did not correlate significantly with age of onset (partial r = −.05, p = .723) or duration (partial r = .05, p = .721) of IED in IED subjects. Also, mean composite FL-GMV values did not significantly differ as a function of the presence (−.05, 95% CI −.28 to .19) or absence (.01, 95% CI −.11 to .13) of lifetime exposure to psychotropic medication ($F_{1,162}$ = .19, p = .663), differences in state depression or anxiety scores (Supplement 1), or differences in history of mild to moderate head injury with or without loss of consciousness (Supplement 1) in all subjects. Although raw composite FL-GMV values correlated with Child Trauma Questionnaire scores (r = −.26, n = 109, p = .006), no significant relationship was noted after controlling for age, sex, race, and education (partial r = −.09, p = .367).

DISCUSSION

The results of this study demonstrate that impulsive aggressive adults with IED as defined by DSM-5 have reduced gray matter volume in frontolimbic structures compared with HC subjects and PC subjects. These frontolimbic structures included cortical (OFC, mPFC, ACC) and subcortical (amygdala, insula, uncus) regions of interest. Across all subjects,

gray matter volume in these regions was inversely correlated with measures of aggression as a dimension, suggesting that although this relationship is dimensional, a threshold level of aggression may be necessary before this difference becomes clinically meaningful. This idea is supported by the observation that although composite aggression scores are inversely related to FL-GMV values regardless of diagnostic group, the presence of IED (rather than aggression score) more fully accounts for the variability in FL-GMV values across subjects. Overall, these findings are consistent with dysfunction in frontolimbic circuits and their relationship with aggression in humans and other primates (22).

These results are consistent with other studies of variously defined "aggressive" individuals, although this is the first study focusing on impulsive aggression and defined by DSM-5 criteria for IED. Specifically, lower volumes in frontal lobes (2); ACC and orbito-mPFC (23); hippocampus, parahippocampal gyrus, uncus, and amygdala (3); hippocampus (5); and hippocampus and amygdala (6) were reported in subjects with borderline personality disorder, who are more aggressive than subjects without borderline personality disorder, although not as aggressive as IED subjects unless they also meet the criteria for IED (1). Other studies in "aggressive" individuals reported reductions in gray matter volume in anterior insula and amygdala (24) and hippocampus (25). Relevant to antisocial disorders and psychopathic personality, violent offenders scoring high in psychopathy were reported to have reduced amygdala volume (26), whereas another study reported reduced cortical gray matter volume in subjects with antisocial personality disorder (7).

Differences in gray matter volume were not accounted for by total intracranial volume; by white matter volume; or by differences in demographic features, age of onset or duration of IED, lifetime history of exposure to psychotropic medication, current or lifetime psychiatric or personality disorder, or levels of state depression or lifetime history of head injury or loss of consciousness. Moreover, these differences were not accounted for by comorbidity with borderline or antisocial personality disorder or by comorbidity with psychopathic personality as defined by the Psychopathy Checklist: Screening Version despite the fact that these comorbidities are thought by some to rule out the diagnosis of IED (1). Although self-directed aggression in the form of history of suicidal attempts, but not self-injurious behavior, was not associated with a reduction in frontolimbic gray matter volume, the sample size of subjects with these histories was small, and a negative finding in this regard is not surprising.

The cause of reduced gray matter volume in subjects with IED and impulsively aggressive subjects is unknown, although these results suggest the presence of a deleterious effect on neuronal processes within these structures. Evidence for this possibility comes from animal studies demonstrating that chronic stress, which is associated with reductions in size of limbic structures, is associated with an increase in the packing density of glia and neurons (27) and with reduction in the arborization of neuronal processes (28). Because the gray matter volume values for these frontolimbic areas were unrelated to the age of onset or duration of IED, lifetime exposure to psychotropic medication, or history of mild head injury, the reductions in gray matter volume observed are more likely related to the fundamental neurobiology of aggression rather than to the clinical presentation at the time of scan, factors related to chronicity, or the degree of prior psychotropic medication exposure. The fact that problematic impulsive aggressive behavior begins early in life and persists throughout life (29) suggests a genetic or a gene-environment interaction that affects the developing brain so that brain regions and circuits involved in impulsive aggression do not develop normally. Genetic factors underlying impulsive aggression have been appreciated for some time and include evidence of substantial genetic influence for aggression and impulsivity (11) and increased family risk of IED among relatives of subjects with IED (10).

Environmental factors associated with the development and maintenance of impulsive aggression include evidence demonstrating that history of childhood trauma is associated with aggression (30) and IED (31) and with reductions in frontolimbic volumes and gray matter density (32). However, in the present study, a measure of childhood trauma did not correlate with gray matter volume after controlling for age, sex, race, and education. Only 65% of the sample had such data, and it is possible such a relationship may have been observed if all subjects had completed this measure. Other possibilities include the impact of learning and early environmental influences, including the modeling of behavioral and emotional dyscontrol, and the impact of poor regulation of emotions and chronic stress, both of which may alter the gray matter volume in these frontolimbic regions. Finally, the basis of frontolimbic volume reduction could be distinctive across diseases and psychiatric disorders, and, given our limited knowledge in this area, the etiologic possibilities may be quite broad.

The strengths of this study include a well-characterized sample of subjects with impulsive aggression and control subjects, validated measures of aggression and impulsivity, and the assessment of several relevant variables that could confound these findings. Inclusion of PC subjects with a higher life history of aggression than HC subjects and with comorbidities largely similar to IED subjects is an additional strength because it enables a dimensional examination of the data as well as examination whether reduced frontolimbic volumes are simply related to the presence of a psychiatric disorder. Limitations include the fact that this is a cross-sectional study and no causal conclusions can be made from associative analyses. Second, ascertainment of subjects may limit the generalizability of these findings in that this study involved subjects who volunteered for a research study rather than for clinical treatment. However, at least half of the IED subjects and PC subjects reported a past history of formal psychiatric evaluation or treatment, and frontolimbic gray matter volume did not differ between subjects with or without this history.

In conclusion, we report a reduction in gray matter volume in six frontolimbic brain regions of subjects with IED compared with HC subjects and PC subjects. This relationship was not accounted for by any of the potentially confounding factors studied or by any comorbidity with other psychiatric or personality disorders. These data are consistent with the posited role of frontolimbic circuits in the pathophysiology of aggression (22).

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