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A multivariate approach to aggression and the orbital frontal cortex in psychiatric patients

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Abstract

The association between orbital frontal cortex (OFC) volume and aggression was investigated in an at-risk psychiatric population. Forty-one psychiatric patients were referred for magnetic resonance imaging and a standardized psychometric assessment of aggression (Lifetime History of Aggression-Revised). Nineteen matched controls had lower levels of aggression and greater OFC volume, establishing the appropriateness of the psychiatric group for studying aggression pathophysiology. Consistent with study hypotheses, left OFC gray matter volume predicted 34% of the variance in self-reported aggression ratings. When impulsivity was not controlled for, left OFC gray matter only accounted for 26% of aggression variance, suggesting a complex relationship between impulsivity and OFC–aggression pathophysiology. Contrary to study hypotheses, right OFC gray matter volume did not predict degree of aggressive behavior. Current models do not account for lateralization, yet this may be quite important. Greater consideration should be given to laterality in OFC regulation of social/emotional behavior. Regulatory focus theory, positing two motivational systems, promotion and prevention, lateralized to the left and right hemispheres, respectively, may provide an explanatory framework for these results. Dysregulation of the left hemisphere 'promotion' motivational system may help to explain the aggressive behavior present in psychiatric populations.

Keywords: Community violence; Neuropsychiatry; Impulsivity

1. Introduction

While knowledge of the association of orbital frontal dysfunction and aggression has historically stemmed from neurologic lesion populations (e.g., Grafman et al., 1996), there is increasing scholarship concerning this

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relationship in psychiatric populations (e.g., Raine et al., 1997). Our group previously reported rightward OFC asymmetry was associated with aggression in a small diagnostically heterogeneous group ($n=15$) of psychiatric patients (Antonucci et al., 2006). The present study focuses on aggression in a larger sample that incorporates a non-psychiatric comparison group ($n=19$) and 26 additional psychiatric participants ($n=41$), to support a multivariate analysis. The subtext for our approach is that other aggression investigations have treated the prefrontal cortex as a whole (Raine et al., 2000), or they have investigated specific prefrontal sub-division contributions to aggression in normal controls (Asahi et al., 2004; Meyer-Lindenberg et al., 2006), or those with acquired neurologic lesions (Berlin et al., 2004). Consequently, less has been known about the specific neural circuitry of aggressive and impulsive behavior within the neuropsychiatric clinic where it is likely to occur, although this work is emerging with schizophrenia (Hoptman et al., 2002; Hoptman et al., 2005; Kumari et al., 2006).

Prefrontal dysfunction is involved in the aggressive and impulsive behavior of neurologic and psychiatric patients (Barratt, 1994; Giancola, 1995; Volavka, 1995, 1999; Grafman et al., 1996; Raine et al., 2000; Brower and Price, 2001; Aron et al., 2004). Rolls (2000) has described euphoria, irresponsibility, and lack of affect as symptoms of orbital frontal damage. Brower and Price (2001) have listed impaired social judgment, risk-avoidance, and empathy as characteristics of focal damage to the orbital frontal cortex (OFC). Heightened levels of aggression and impulsivity are linked with specific psychiatric conditions, such as psychosis, anti-social personality disorder, and substance abuse (Pihl et al., 1993; Barratt, 1994; Bauer et al., 1994; Eronen et al., 1998; Moeller et al., 2001; Berlin et al., 2004). Individuals with low executive cognitive function, such as those with anti-social personality disorder, may fail to internalize inhibitory influences (Lau et al., 1995). Furthermore, the combination of mental illness and substance abuse confers particular risk for aggressive behavior (Soyka, 2000). Therefore, robust relations between aggressive and impulsive phenomena and brain substrates may be as likely to occur within a dual diagnosis psychiatric as a neurologic population. Indeed, some have advocated investigating the neural bases of emotional disorders across DSM-IV categories (Breiter and Gasic, 2004). Relating the pathophysiology of aggression to specific prefrontal regions has important implications for assessment, treatment, and rehabilitation.

The prefrontal cortex (PFC) is a critical substrate for motoric, behavioral and complex cognitive processes, so much so that parcellation of 11 sub-regions (Crespo-Facorro et al., 1999) has been proposed. However, a simpler dichotomy may be preferable, with the dorsolateral region a substrate for cognitive function (DLPFC: e.g., Berlin et al., 2004) and the orbitofrontal region (OFC) a substrate for emotional or social behavior (Fuster, 1990, 2000; Dias et al., 1996; Bechara et al., 1998; Bechara et al., 2000; Giancola, 2000; LeDoux, 2002; Happaney et al., 2004). Executive control of social behavior is presumed to be represented in the orbital and medial frontal cortex via the synthesis of emotional and cognitive information (Beer et al., 2004). According to the somatic marker hypothesis (Bechara et al., 2000), the OFC serves as the convergence zone for the representation of bioregulatory states (including emotions) and factual knowledge. Therefore, it is the area of the brain in which decision making is influenced by feeling states. According to Rolls (2000), the OFC is involved in emotion by controlling reward-related and punishment-related behavior, and is thought to represent reward values and learning reinforcement associations and contingencies (Rolls, 1999). Consistent with these theoretical reviews, research has demonstrated abnormal responses to emotional stimuli following OFC lesion (Rolls et al., 1994; Bechara et al., 2000), as well as differential OFC activation during emotionally valenced tasks (Blair et al., 1999; Rule et al., 2002).

In an important empirical report on the pathophysiology of aggression, Grafman et al. (1996) demonstrated that veterans with lesions to the ventro-medial cortex and the OFC were reported to have more aggressive behavior than veterans with other lesion locations. OFC dysfunction is thought to produce aggression via a low activation threshold for negative affect (Davidson et al., 2000), or by emotional dysregulation (Giancola, 1995; Blair, 2001). Davidson et al. (2000) argue for the role of the OFC–amygdala network in aggression. They have proposed an inability to suppress negative emotion as a core factor in aggression. Dysregulation of the amygdala and ventromedial PFC has been linked to the pathophysiology of depression with anger attacks (Dougherty et al., 2004). This is consistent with Blair's emotional dysregulation view and suggests an emotionally disinhibited sub-type of aggression. While many experts maintain the role of the OFC in aggressive behavior, alternatively, some have argued for the dorsolateral PFC as the substrate for aggressive behavior and the OFC as the substrate for "disinhibited-nonaggressive" behavior (Giancola, 1995).

In models of OFC and amygdala control of social and/or aggressive behavior, laterality is not given major consideration, though the lateral–medial and anterior–

posterior OFC dimensions are. For example, Bechara et al. (2000) devoted considerable attention to the anterior–posterior extent of OFC lesions, with those involving the whole length of the OFC more likely to impact on decision making and memory. Blair (2007) considers medial OFC connections to the amygdala more critical in regulating social behavior than lateral connections. Hornak et al. (2004) concluded unilateral OFC lesions were insufficient to produce the deficits in reward-related reversal learning observed with bilateral OFC lesions, and that bilateral involvement was critical to the capacity to guide behavior on the basis of the reward value of stimuli. Nevertheless, recent studies indicate that lateralization of function could play a role in aggression and impulsivity. Specifically, whereas the left hemisphere was involved in aggression during an induction protocol in a functional magnetic resonance imaging (fMRI) study of depressed patients (e.g., Dougherty et al., 2004), the right inferior frontal cortex was involved primarily in the context of behavioral inhibition in a review of lesion studies (Aron et al., 2004). These authors propose a model of action and inhibition in which cerebral lateralization plays a strong role, with the right hemisphere contributing inhibitory processes. Indeed, a recent investigation with fMRI and healthy controls found a negative correlation between motor impulsiveness and activation related to the No-Go task in the right dorsolateral PFC (Asahi et al., 2004).

Several recent studies have begun to explore the relationship of OFC structure to aggression in schizophrenic patients. Specifically, in a group of 14 men with schizophrenia using diffusion tensor imaging (DTI), five points on a dorsal to ventral axis in the PFC were analyzed in relation to measures of impulsivity and aggression, and only the ventral most point (below the AC-PC line) in the right hemisphere was significantly related to those behaviors (Hoptman et al., 2002). Drawing on Davidson's valence hypothesis, these investigators posited that dysregulation of avoidance mechanisms in the right hemisphere produced a vulnerability to aggression and impulsivity. More recently, OFC volumes of institutionalized schizophrenic patients were correlated with scores on the Overt Aggression Scale, a measure of aggression used on hospital units, with greater left OFC gray matter volume and left and right OFC white matter volumes associated with higher overall levels of aggression (Hoptman et al., 2005). Further, an fMRI working memory comparison of 13 seriously violent and 12 not seriously violent schizophrenic participants found reduced right inferior parietal activation among the violent schizophrenic participants (Kumari et al., 2006). While the authors noted frontal lobe dysfunction is classically associated with behavioral problems such as violence, they suggested that their findings could reflect a disruption in frontal and parietal neural networks governing attention. The present investigation is designed to contribute to this literature regarding the relationship of brain structure and aggression.

To summarize, OFC lesions have long been associated with aggression in neurologic patients, OFC microstructure abnormalities have been linked to aggression and impulsivity in schizophrenia, and amygdala–OFC network abnormalities may be a basis for sociopathy and anger attacks in major depression. Notably, more work is needed to understand the putative role of OFC dysfunction among the general psychiatric population in which aggressive and impulsive behaviors are common.

The OFC was operationally defined based on a previously published protocol (Crespo-Facorro et al., 1999) applied in our laboratory (Antonucci et al., 2006).

The following two goals were set for this clinical investigation:

(1) Establish the appropriateness of the psychiatric group for the study of the neuropathophysiology of aggression by comparing it with controls on a psychometric measure of aggression and volumetry measurement of the OFC.
(2) Develop an understanding of the neuropsychobiology of the dependent variable, aggression, by predicting its value with left and right OFC volumes, and relevant demographic factors. Based upon our previous finding of rightward OFC asymmetry associating with aggression, we predicted a negative correlation of left OFC gray matter and a positive correlation of right OFC gray matter with aggression.

2. Methods

2.1. Participants

Eighty-four male and female psychiatric patients were referred for neuropsychiatric evaluation and treatment from the acute inpatient service at Tufts Medical Center (TMC) or the outpatient clinics of TMC or Lemuel Shattuck Hospital (LSH), of whom 41 met criteria for study inclusion (see Table 1 for demographics). The project has been ongoing over a 5-year period, and scanners have changed; the first 18 participants were imaged on a Siemens machine and the remaining 23 on a General Electric machine. Nineteen community-dwelling participants free of psychiatric illness constituted a comparison group. The primary psychiatric diagnosis,

Table 1
Participant demographics

Variable	Psychiatric group ($n=41$)	Non-psychiatric group ($n=19$)	P-value for t-tests or chi square
	Mean (S.D.)	Mean (S.D.)	
Age	40.12 (8.3)	40.94 (7.5)	0.71
Education	10.80 (2.9)	15.53 (1.9)	0.00 *
Gender	5/36 (female/male)	1/18 (female/male)	0.37
Handedness	8/26 (left/right) [a]	3/16 (left/right) [a]	0.39

* $P<0.01$.
[a] Handedness data unavailable on 7/41 psychiatric patients.

using DSM-IV criteria, was obtained from chart review, based upon the structured psychiatric interview of the psychiatric contributor (CF) or his colleagues. Patients primarily presented with serious mental illness, and were stabilized in a multi-disciplinary psychiatric rehabilitation approach at the time of work-up. MRI was performed as part of the neuropsychiatric evaluation, and scans were reviewed for clinically significant findings. Each participant underwent an informed consent procedure; psychiatric participants gave informed consent to have their clinical data used for research purposes; the comparison group gave permission to undergo psychometric evaluation and head MRI. The study was approved by the Investigational Review Boards at TMC, LSH, and Suffolk University.

2.1.1. Exclusion criteria

Exclusion criteria for all participants were sensory and/or motor deficits precluding participation, non-English speaking, history or indication of mental retardation or dementia, evidence of obvious neuropathology other than atrophy on MRI, head injury with loss of consciousness greater than 1 h, and contraindication for MRI (metal in head, cardiac pacemaker, etc.). Additional exclusion criteria for the non-psychiatric comparison group were: major Axis 1 diagnosis, history of problems with aggression, anger, or impulse control, history of substance abuse, and family history of major Axis 1 diagnosis.

2.1.2. Psychiatric participants

Of 84 consecutive referrals, 41 were missing data points, typically due to failure to attend appointments, and two presented obvious neuropathology on MRI (right frontal encephalomalacia, white matter pallor secondary to HIV), leaving 41 psychiatric participants for study. Primary psychiatric diagnoses were as follows: schizophrenia or schizoaffective disorder = 9, bipolar affective disorder = 10, unipolar affective disorder = 13, anxiety disorder = 3, attention deficit/hyperactivity disorder = 5, alcoholism = 1. Sixteen of the 41 participants met DSM-IV criteria for alcohol abuse or dependence based on chart review, 22 did not meet criteria, and for 3 participants there was insufficient chart information to make a determination.

2.1.3. Community-dwelling participants

The non-psychiatric group was recruited through advertisements placed in Boston newspapers and on the internet.

2.1.4. Demographic characteristics/matching (see Table 1)

The psychiatric group averaged 40.1 years of age, and 10.8 years of education, 36/41 were male and 8/34 were non-right-handed (handedness data were unavailable in 7 participants). Age, gender, and handedness did not differ significantly between groups, while level of education was significantly higher in the non-psychiatric group (averaging 15.5 years of education), as it was difficult to recruit less educated controls.

2.2. Procedures

Psychiatric participants were administered the Lifetime History of Aggression Scale-Revised (LHA-R; Coccaro et al., 1997) within 2 weeks of undergoing MRI. The LHA-R subscales for verbal/physical aggression (LHA-R Agg), consequences of anti-social behavior (LHA-R CAB), and self-directed aggression (LHA-R SDA) were derived. The Barratt Impulsivity Scale (BIS; Patton et al., 1995) was administered to control for trait impulsivity, and its subscale scores were calculated (no planning — BIS-NP, cognitive — BIS-Cog, motor — BIS-Mtr). See Table 2 for descriptive statistics.

Table 2
Aggression psychometrics

Subscale	Psychiatric group ($n=41$)	Non-psychiatric group ($n=19$)	F-value	P-value
	Mean (S.D.)	Mean (S.D.)		
LHA-R Total	26.52 (13.17)	9.84 (6.78)	6.1	0.02 *
LHA-R Agg	13.98 (6.83)	7.58 (4.75)	2.0	0.16
LHA-R CAB	10.28 (5.84)	2.15 (2.52)	9.1	0.00 **

ANCOVA and MANCOVA, co-varying education level.
Note. LHA-R = Lifetime History of Aggression Scale-Revised; LHA-R Agg = subscale for verbal/physical aggression; LHA-R CAB = subscale for consequences of anti-social behavior.
* $P<0.05$.
** $P<0.01$.

2.2.1. MRI acquisition

Eighteen psychiatric patients underwent MRI at TMC on a 1.5 T Siemens Symphony magnet (Siemens, Iselin, NJ) using the following scanning protocol: (1) three-dimensional (3D) Magnetization Prepared Rapid Acquisition Gradient-echo (MPRAGE) coronal images with TR=11.1 ms, TE=4.3 ms, slice thickness/interslice gap=1.5 mm/0 mm, matrix=256×256, field of view=25 cm^2, flip angle 15°, and acquisition time of 6 min; (2) conventional dual-echo proton density and T2-weighted images with TR=2230 ms, TE1=20 ms, TE2=80 ms; field of view=23 cm^2; slice thickness=5 mm, no gaps; matrix=256×256; and acquisition time of 6 min 30 s. The research plan called for all participants, psychiatric and control, to be scanned at TMC. However, it became apparent that psychiatric participants from LSH were much more likely to make appointments if the scan was conducted on site. Therefore, the remaining 23 psychiatric participants were imaged at LSH on a 1.5 T General Electric Signa Excite scanner (GE, Milwaukee, WI) using the following scanning protocol: (1) three-dimensional (3D) Spoiled Gradient-Recalled (SPGR) coronal images with TR=33 ms; TE=3–19 ms, slice thickness/interslice gap=1.5 mm/0 mm, matrix=256×256, field of view=25 cm^2, flip angle 35°, and acquisition time of 5 min 30 s; (2) conventional dual-echo proton density and T2-weighted images with TR=2500 ms, TE1=30 ms, TE2=90 ms; field of view=24 cm^2; slice thickness/interslice gap=5 mm/0 mm; matrix=256×256; and acquisition time of 6 min.

2.2.2. Image processing

Data processing has been previously described (Antonucci et al., 2006).

2.2.3. ROI tracing protocol

The OFC was traced in the coronal plane and the protocol has been described previously (Antonucci et al., 2006). Inter-rater reliability determination was different in this study. The senior author reviewed each brain sample and established parameters based on neuroanatomic landmarks separating the OFC from the inferior frontal gyrus laterally and the straight gyrus medially. Specific landmarks included the beginning of the OFC with the emergence of the fronto-marginal sulcus, the emergence of the olfactory sulcus and lateral orbital sulcus, the inferior aspect of the circular sulcus of the insula, and the last slice on which the medial and/or posterior orbital gyrus could be reliably traced. The left and right OFC were then traced manually by either the senior author or one of two trained undergraduate tracers. Inter-rater reliability, for the left OFC, of the two undergraduate tracers with the senior author was acceptable (tracer 1 $r=0.87$, $P=0.00$; tracer 2 $r=0.76$, $P=0.00$).

Total intra-cranial volume (TICV) was calculated on the T2-weighted images based upon an established protocol (Blatter et al., 1995). Volumetry results are presented in Table 3.

Table 3
Brain volumetry, MANCOVA, co-varying years of education and BIS-Mtr

Region	Psychiatric group ($n=41$)	Control group ($n=19$)	F-value	P-value
	Mean (S.D.)	Mean (S.D.)		
TICV (cc)	1396 (134.6)	1511 (157.1)	4.26	0.02
Left OFC (cc)	14.12 (2.68)	17.18 (1.69)	10.64	0.00
Right OFC (cc)	14.23 (2.88)	17.06 (1.31)	9.49	0.00

Note. TICV = total intra-cranial volume; OFC = orbitofrontal cortex.

3. Results

Pre-analysis of data revealed regions of interest ROIs, as well as aggregate and subscale psychometrics free of outliers and normally distributed in each group, with the exception of LHA-R SDA which was comprised of only two items, and was removed from further analysis.

3.1. Aggression and volumetry in psychiatric patients versus controls

LHA-R Total was subjected to ANCOVA, and LHA-R Agg and LHA-R CAB were subjected to MANCOVA, controlling for level of education (see Table 2). Aggregate aggression scores, and the consequences of antisocial behavior subscale, controlling for level of education, were substantially higher in the psychiatric group. After controlling for education level, the quantity and frequency of physical and verbal aggression was not higher in the psychiatric group. Left and right OFC, and TICV were smaller in the psychiatric group after controlling for differences in years of education (see Table 3).

3.2. Prediction of aggression with ROIs in the psychiatric group

The pre-analysis correlation matrix suggested that the LHA-R Agg subscale, measuring physical and verbal aggression, would produce the best prediction. The partial correlation of left OFC and LHA-R Agg, controlling for

TICV, was statistically significant ($r=-0.48$, $P=0.00$) while that of the right OFC was not ($r=-0.23$, $P=0.14$); however, the difference between the two correlation coefficients was not statistically significant (Fisher's $z=1.26$, $P=0.11$). The bivariate Pearson correlation of the left and right OFC was very high ($r=0.86$, $P=0.00$), and it was the case that total OFC volume was associated with aggression ($r=-0.59$, $P=0.00$). Therefore, the partial correlation of each OFC was considered while co-varying out years of education, BIS-Mtr, and the opposite side of the OFC. With that analysis a robust relationship of the left OFC and LHA-R Agg was observed ($r=-0.59$, $P=0.00$), and no significant association was found for the right OFC ($r=0.28$, $P=0.08$). The difference between those two correlation coefficients was statistically significant (Fisher's $z=-3.92$, $P=0.00$), providing a rationale to proceed with linear regression of the left OFC upon LHA-R-AGG-R. No further analysis of the right OFC was conducted, as there was a lack of support for the initial hypothesis of a positive correlation of right OFC and aggression.

For linear regression pre-analysis, LHA-R Agg was correlated with subject variables (age, education, TICV, impulsivity) to explore potential confounds. Of those, Pearson bivariate correlations with LHA-R Agg revealed it was significantly negatively correlated with years of education ($r=-0.37$, $P=0.02$), and BIS-Mtr ($r=0.30$, $P=0.05$). Age and TICV were not significantly related. The lack of association of TICV and aggression helps to rule out the influence of non-specific atrophic factors in the data set. Among the BIS subscales, the BIS-Mtr subscale was most highly correlated with LHA-R Agg ($r=0.30$, $P=0.054$), a finding reported in other psychiatric investigations (Monahan et al., 2000). Gender did not significantly correlate with level of aggression, and while men typically have higher levels of aggression (e.g., Monahan et al., 2000), the forensic nature of this sample likely produced a general elevation. Handedness had no significant impact on OFC volume, TICV, or aggression, based upon independent samples *t*-tests.

Table 4
Linear regression upon LHA-R Agg: a model summary

Model	Adjusted *r* square	Std. error of the estimate	*r* square change	*F* change	*df* 1,2	Sig. *F* change
1	0.114 (a)	6.42	0.137	6.17	1,39	0.017
2	0.214 (b)	6.05	0.117	5.94	1,38	0.020
3	0.555 (c)	4.55	0.335	30.13	1,37	0.000

a Predictors: (constant), education.
b Predictors: (constant), education, BIS motor.
c Predictors: (constant), education, BIS motor, left OFC.

A stepwise linear multiple regression was conducted on LHA-R Agg with the following predictors entered in three steps — education, motor impulsivity, and left OFC gray matter volume (see Table 4). Individually, each of the three steps was predictive of LHA-R Agg at a statistically significant level, and all three predictors together accounted for 55% (based on adjusted *r* square) of the variance in LHA-R Agg. After variance was accounted for by motor impulsivity and education level, left OFC gray matter volume accounted for 33% of the remaining variance in LHA-R Agg. The tolerance values for the collinearity statistic were all above 0.9. Education and brain volume values were not associated with one another (Pearson bivariate correlations: left OFC $r=-0.07$, right OFC $r=-0.18$, TICV $r=0.06$), nor was BIS-Mtr meaningfully associated with volumetry (Pearson bivariate correlations: left OFC $r=0.17$, right OFC $r=0.23$, TICV $r=0.15$).

Men trended toward having larger TICV (two-tailed $t=1.94$, $P=0.06$). Examining gender differences in OFC volume by ANCOVA, with TICV as the covariate, the female left and right OFC emerged as larger for the five female participants (left OFC *F*-value=8.08, $P<0.05$; right OFC *F*-value=7.01, $P<0.05$), an effect that has been previously reported (Cowell et al., 2007). Removing the females and re-performing the linear regression analysis yielded a very similar overall model (adjusted *r* square=0.59), with the only difference being education on step two. This was reduced from a significant effect to a trend (significance of *F* change=0.07). Although SPGR-derived ROIs were slightly smaller than MPRAGE-derived ROIs, the differences in derived volume did not reach the level of statistical significance. When scan type was added as the first step in the regression model, adjusted *r* square for that variable was 0.00, and the adjusted *r* square values for education, BIS-Mtr and left OFC were virtually unchanged from the values presented in the previous section. Participants were divided into those meeting DSM-IV criteria for alcohol abuse or dependence ($n=16$) or not meeting those criteria ($n=22$; in 3 cases a determination could not be made) on the basis of a chart review. Alcohol misuse status was not associated with aggression level or ROI volume.

3.3. Impact of diagnosis (Spearman's rho bivariate correlations)

The correlation of left OFC and LHA-R Agg was run for each diagnostic group, to determine the impact of diagnosis. Given the small numbers in each group, the coefficients are provided as descriptive, not inferential statistics. There were three psychiatric participants

whose diagnoses (e.g., PTSD) did not fit into one of the following groups, and were excluded from this analysis. The association of left OFC and LHA-R Agg was strong in schizophrenic ($n=9$, $r=-0.64$), depressive ($n=12$, $r=-0.68$) and ADHD groups ($n=5$, $r=-0.7$) but not in bipolar participants ($n=12$, $r=-0.22$). This demonstrated a fairly consistent association of left OFC and LHA-R Agg, with the possible exception of bipolar affective disordered participants.

3.4. Prediction of aggression with ROIs in the control group

The bivariate Pearson correlation coefficients of LHA-R Agg and left and right OFC revealed the absence of significant association ($r=-0.21$, $P=0.38$, $r=-0.00$, $P=0.99$, respectively). Partialing out education and BIS-Mtr levels did not meaningfully change the pattern of correlation.

In summary, a specific and significant negative association of left OFC volume and aggression was found among psychiatric participants consistent with initial hypotheses, while the predicted positive association of right OFC volume and aggression was not statistically significant. No association of volumetry and aggression was found among non-psychiatric controls.

4. Discussion

In neurologic patients, aggression is a known correlate of orbital lesions (i.e., Grafman et al., 1996). In sociopathy, disruption of the amygdaloid–OFC network is the presumed basis for the empathy deficit (Blair, 2007). However, less work has been done on the pathophysiology of aggression amongst the general psychiatric population. This heterogeneous group of psychiatric patients displayed a pathophysiology for aggression on psychometrics and volumetrics when compared to matched community-dwelling controls. The hypothesized negative correlation of aggression and the left OFC was confirmed, and while the predicted positive correlation of right OFC and aggression was found, that relationship was not statistically meaningful. Among the various diagnostic groups included here, the systematic association of aggression and the left OFC appeared to apply to all patient groups except bipolar affective disorder participants. Further, an OFC–aggression relationship was not found in the controls, possibly due to the restricted range of both volumetry and aggression psychometrics, or the absence of a pathophysiology. This work also extends in a more neuroanatomically specific fashion, to reports of generalized volume reductions in the prefrontal cortex in similar populations, namely, in individuals with anti-social personality disorder (Raine et al., 2000). While in neurologic populations bilateral OFC lesions have been found necessary to produce the type of deficits associated with social dysfunction (Hornak et al., 2004), in this sample, after co-varying education, impulsivity, and opposite side OFC volume, only reduction of left OFC volume emerged as a significant substrate for aggression.

After 25% of the variance in physical/verbal aggression was accounted for by education and motor impulsivity (14 and 11%, respectively), left OFC volume accounted for 34% of the remaining variance. The robust association of left OFC volume and aggression, suggests a role of the left OFC in emotional and/or instrumental types of aggression. The result parallels that of Hoaken et al. (2003) in which impulsivity was found in aggressive individuals with low executive cognitive functioning, but was not thought to be the best explanation for aggression. Given the slower reaction times of more highly aggressive participants, the authors favored an 'interruption of social information processing' explanation of aggression. This finding runs contrary to some thinking (e.g., Berlin et al., 2004), in that 'fundamental impulsiveness' did not contribute to the OFC–aggression association found here. Dougherty et al. (2004) presumed that their major depressives prone to anger attacks were manifesting impulsive aggression without measuring impulsivity. However, in this investigation, the left OFC–aggression association was stronger after impulsivity was accounted for. Therefore, the neural basis of impulsivity may be somewhat dissociable from the left OFC and aggression or may interact with aggression. In fact, Aron et al. (2004), in asserting a localisationist approach to PFC function, argue for a critical role of the right IFC (inferior frontal cortex) in cognitive inhibition. These interpretations would suggest that understanding the neural bases of socially inappropriate behavior may require a consideration of the interplay of the orbital and inferior frontal cortices.

The negative correlation of left OFC gray matter volume with LHA-R Agg, assuming the OFC is a substrate for executive control of social and or emotional behavior, suggests that volume reduction is related to problems regulating social behaviors, consistent with the explanation offered by Hoaken et al. (2003). In concordance with the present findings, a recent neuropsychiatric study of major depression with or without anger attacks implicated only the left ventro-medial PFC (Dougherty et al., 2004). During an anger induction paradigm, those investigators found that participants with major depressive disorder with anger attacks

manifested simultaneously increased activation in the left amygdala and VMPFC, while for controls and major depressives without anger attacks, amygdala and VMPFC activation were inversely related. Those prone to anger attacks appeared to lack the mutually inhibitory properties of OFC and amygdala interaction. Emotional dysregulation (Blair, 2001) or 'deactivation of negative affect' (Davidson et al., 2000) explanations have also been offered for OFC dysfunction. For example, among healthy controls the medial OFC (L>R) was found to become deactivated during unrestrained imaginal aggression scenarios (Pietrini et al., 2000). Further, a recent frontal lobe lesion study found a critical deficit in processing social schemas among left frontal, but not right frontal lobe, participants (Goel et al., 2004). It should be pointed out that other recent important work has reported a specific relationship between right OFC, and not left OFC, white matter and aggression and impulsivity (Hoptman et al., 2002), and developed a dysregulation of avoidance mechanism explanation of their finding.

Given the specific left OFC involvement, lateralizing explanatory mechanisms appear appropriate. Regulatory focus theory (RFT; Higgins et al., 1997) involves two social-cognitive motivational systems, and may explain higher order strategic aspects of motivation. RFT is similar to the concept of the behavioral inhibition and activation system (BIS/BAS; Davidson, 1992) that involves aversive and appetitive motivational states and spatial/temporal aspects of avoidance and approach; however, RFT may be more appropriate given the complex nature of aggression. In RFT, the *promotion system* is associated with approach motivation and a focus on 'ideal' goals, while the *prevention system* is associated with avoidance motivation and 'ought' goals (Amodio et al., 2004). Implicit regulatory focus measured by reaction time to 'ideal' and 'ought' words was associated with asymmetrical frontal cortical activity on EEG (Amodio et al., 2004). Promotion focus was positively correlated with left prefrontal and negatively correlated with right prefrontal activation, while the inverse pattern was found for prevention focus. A recent fMRI investigation of RFT also offered some support for the putative lateralization (Eddington et al., 2007). Under RFT, one could posit the left OFC–aggression connection as a dysregulation of the promotion system that could reflect difficulty achieving 'ideal-type' goals or in managing experienced frustration when a discrepancy between ideal-goals and actual circumstances arises.

The absence of aggression sub-typing was a limitation of this investigation, resulting in some speculation regarding type of aggression and OFC lateralization. Further, for logistical reasons, two different types of imaging protocols were used, potentially impacting the homogeneity of brain image analysis processing; however, analyses did not demonstrate a statistically significant difference between the imaging groups.

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