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Orbitofrontal correlates of aggression and impulsivity in psychiatric patients

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Abstract

The association between orbital frontal cortex (OFC) volume and aggression and impulsivity was investigated among a heterogeneous group of non-psychotic psychiatric clients. Fifteen non-psychotic subjects from two different psychiatric clinics (New England Medical Center and Lemuel Shattuck Hospital) with a variety of diagnoses were sequentially referred for magnetic resonance imaging (MRI) for clinical purposes. This convenience sample, clinically stable at the time of evaluation, received a standardized psychiatric diagnostic interview, aggression and impulsivity psychometrics (Barratt Impulsivity, Lifetime History of Aggression, and Buss-Perry Aggression scales), and an MRI protocol with image analysis. OFC gray matter volume, total as well as left and right, was significantly and positively associated with motor impulsivity. OFC asymmetry was associated with aggression, though total, left, and right OFC volume measurements were not. For subjects without affective disorder, there was a strong and positive association of the OFC to motor and no-planning subscales of the Barratt Impulsivity Scale. For subjects with affective disorder, there was a strong association of OFC asymmetry to both of the aggression psychometrics. Consistent with expectation, results are suggestive of OFC involvement in the neural circuitry of impulsivity and aggression. The findings suggest a dissociation of the role of the OFC in relation to aggression and impulsivity, such that the OFC may play a part in the regulation of aggressive behavior and a generative role in impulsive behavior.

Keywords: Magnetic resonance imaging; Personality; Barratt Impulsivity Scale

1. Introduction

The association between mental illness and aggression has long been established (Eronen et al., 1998), particularly when major mental illness combines with substance abuse (Soyka, 2000). The interaction of

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multiple, complex biological factors, such as brain lesions, neurophysiologic dysfunction and the contribution of neurochemical systems, are posited to influence the neurobiological basis of aggressive behavior (Eichelman and Hartwig, 1996; Kavoussi et al., 1997). Neuroanatomical models of brain circuitry involved in aggression consistently implicate an interconnected network of regions that includes the frontal lobes and the amygdala along with other brain areas. Many of these models agree on the importance of prefrontal cortical dysfunction (Blair, 2001; Brower and Price, 2001; Davidson et al., 2000; Giancola, 1995; Pietrini et al., 2000; Volavka, 1999), although they may differ as to the localization of dysfunction within that large and complex region of the brain. In a number of these models, dysfunction of the dorsolateral prefrontal cortex (DLPFC) creates a pathway to violence by way of executive dysfunction and consequent problems of meeting occupational/social/academic expectations (Brower and Price, 2001; Giancola, 1995). Impulsivity, acting before thinking, can be considered a form of executive dysfunction in these models, along with other phenomena such as cognitive rigidity (difficulty weighing alternatives) or the inability to generate strategies. Alternatively, it has been posited that dysfunction of the orbitofrontal cortex (OFC) creates a pathway to aggression via emotional dysregulation (Blair, 2001; Giancola, 1995), functional deactivation (Pietrini et al., 2000), impulsivity (Brower and Price, 2001), or a low threshold for activation of negative affect (Davidson et al., 2000). Volavka (1999), incorporating environmental influences, takes a somewhat broader view of a neurobiological typing for violence, which includes the temporal lobe. He proposes two propensities toward violence: one via a genetic predisposition to prefrontal dysfunction (without further localization) leading to impulsive violence, while in another sub-type, an abnormal rearing environment leads to violence via decreased temporal lobe volume.

The involvement of the prefrontal cortex in aggressive and/or impulsive behavior finds support from recent neuroimaging studies. Raine et al. (1997) compared 41 murderers pleading not guilty by reason of insanity to 41 age and sex-matched controls on regional PET activation. They found lower activation in the prefrontal, superior parietal, and angular gyrus regions and no differences in temporal lobe activation. Higher occipital lobe activation was encountered among the murderers during a sustained attention task. Soderstrom et al. (2000) compared violent offenders to normal controls on head SPECT and found reduced perfusion bilaterally in the hippocampus, the left frontal white matter, and the right angular gyrus and mediotemporal region. Research on normal controls also supports an association between the frontal lobe and aggression and may suggest some degree of lateralization as well. For example, Pietrini et al. (2000) found that specific deactivation of the left and right medial frontal gyri was associated with cognitive restraint during experimentally induced aggression scenarios. This area was also described as Brodmann's area 10. During a scenario involving unrestrained aggression, peak deactivation was seen in the left medial frontal gyrus, also described as BA 11. Comparing experimental conditions, functional deactivation of BA 10/11 was strongest when subjects were instructed to express, rather than inhibit, aggressive behavior.

The use of emotion-induction paradigms with psychiatric patients has also led to recent advances in understanding the neurobiology of aggression. Recently, Dougherty et al. (2004) found 10 patients with major depression who were prone to anger attacks had significantly less PET-derived activation in the left ventromedial prefrontal cortex (VMPFC) than either 10 normal controls or 10 major depressive controls not prone to anger attacks. Invoking the neural circuitry of aggression, an association was found between amygdaloid and VMPFC activation. The authors concluded the pathophysiology of major depression with and without anger attacks may be different.

Grafman et al. (1996) explored the relation between penetrating head wounds and aggressive/violent behavior among Vietnam War Veterans and found that veterans with ventromedial-frontal lesions obtained significantly higher scores on a measure of aggressiveness and violence in comparison to veterans with other lesions. In a population characterized by its tendencies to aggression, Raine et al. (2000) found individuals diagnosed with anti-social personality disorder had lower prefrontal gray matter volume (but not white matter) in comparison to psychiatric, substance abuse, and community-based controls. Note Raine's work took the PFC as a whole without reference to subdivisions. Tonkonogy (1991) selected 23 chronic psychiatric patients from a larger group of 87 patients with suspected organic mental disorder. Tonkonogy found lesions of the anterior and inferior temporal lobe were more common in violent patients, and lesions of frontal, parietal or superior temporal lobe were more common in non-violent patients. As pointed out previously, in some aggression neurobiology models, impulsivity is considered a critical factor moderating the connection between OFC dysfunction and aggression (Brower and Price, 2001).

Interestingly, a recent review finds some support for functional localization of inhibition to the right inferior

frontal cortex (IFC; Aron et al., 2004), rather than the DLPFC or OFC. This review favored evidence from advanced lesion-mapping studies localizing inhibition to the right IFC, as opposed to neuroimaging studies that reveal multiple foci. Despite heightened interest in the association of the IFC and impulsivity, there is continued evidence of the association of impulsivity and the OFC coming from recent animal lesion studies. Winstanley et al. (2004) reported a functional dissociation of the basolateral amygdala (BLA) and OFC in impulsive choice in rats. BLA lesions were associated with increased preference for immediate reward, while OFC lesions were associated with increased preference for a larger, delayed, reward. The authors suggest that the BLA encodes incentive value, while the OFC monitors and updates expected outcomes (the OFC-lesioned rats perseverated to their last response). Thus, individuals having difficulty associating environmental contexts to expected outcomes may be vulnerable to both impulsivity and aggression.

A recent lesion study of non-violent neurological patients (Goel et al., 2004) found asymmetrical involvement of the frontal lobes in social reasoning, a function relevant to the study of aggression. These workers found 19 patients with focal frontal lobe lesions performed significantly worse than age- and education-matched controls on the Wason Card Selection Task, specifically when provided with social permission schema, but performed no differently from controls when arbitrary rules were given. Separating patients with right hemisphere lesions from those with left hemisphere or bilateral lesions revealed that right hemisphere patients were no different from controls. The authors concluded that frontal lobe involvement in reasoning is asymmetric, left greater than right, and necessary for reasoning about social situations. Consistent with the results of lesion-based work, a number of neuropsychological investigations link dysfunction of 'PFC' tasks to heightened aggression levels (e.g., Giancola and Zeichner, 1994).

Therefore, research in violent and non-violent, neurological and psychiatric populations, based on activation, volumetric, lesion, and neuropsychological studies, links frontal lobe dysregulation, particularly of the left frontal lobe, to aggression, impulsivity, and/or problems in social reasoning. Activation and lesion studies indicate a fairly specific association of the inferior frontal cortex and aggression and impulsivity as well as suggesting a role for asymmetry/lateralization. The research, however, does not indicate that dysfunction of the PFC alone results in aggressive behavior. Clearly, investigations point to the involvement of the temporal lobes, anterolateral aspects of the parietal lobe, and the amygdala in the neural circuitry of aggression as well as impulsivity. Nevertheless, there is compelling evidence linking the inferior aspects of the PFC to aggression and impulsivity, as well as indications that studying this specific PFC subdivision on its own is worthwhile.

The present study is based on the increasingly substantiated notion that the prefrontal cortex is heterogeneous in function and that investigation of the association between prefrontal subdivisions and aggression and impulsivity is warranted. Previous research has been limited by presenting the PFC as a whole, and little work has been done on the association, or even potential dissociation, between aggression and impulsivity. It is also based on the notion, backed by several studies (Dougherty et al., 2004; Raine et al., 2000), that investigation of the localization of aggression and impulsivity, specifically for mentally ill populations, is feasible and worthwhile. Most studies of aggressive behavior include extremely violent offenders. Little is known about aggressive individuals in a non-institutionalized setting who consistently exhibit aggressive and/or impulsive behaviors, yet have not suffered gross brain damage. The OFC has been posited as critical to the expression of aggression and impulsivity, with indications that the left OFC may be particularly important in the regulation of aggression. It was, therefore, anticipated that a heterogeneous group of non-psychotic psychiatric patients, with a broad range of aggression problems, would provide opportunity for systematic study of the role of the OFC in the neurobiology of aggression and impulsivity. Toward this purpose the following hypotheses were developed for a quasi-experimental clinical study design:

(1) Aggression is associated with decreased volume in the OFC corrected for whole brain volume (WBV).
(2) Impulsivity is associated with decreased volume in the OFC corrected for WBV.
(3) Left OFC volume will be more strongly associated than right OFC volume based on aggression activation studies and lesion effects on reasoning processes.

2. Methods

2.1. Participants

Fifteen clients (see Table 1 for more details) with major or minor mental illness were recruited after referral for MRI from the acute inpatient service at Tufts-New England Medical Center (T-NEMC) or outpatient clinics of T-NEMC or Lemuel Shattuck Hospital. Subjects were

Table 1
Subject demographics

Subject ID#	Intake-interview based diagnosis	Age	Education (in years)	Gender
1	Major depressive disorder	36	12	m
2	Attention deficit/ hyperactivity disorder	43	14	m
3	Major depressive disorder	48	12	f
4	Alcoholism	50	9	m
5	Anti-social personality disorder	43	12	m
6	Bipolar disorder	35	13	m
7	Substance-induced depression	51	12	f
8	Major depressive disorder	41	7	m
9	Major depressive disorder and GAD	36	12	m
10	Post-traumatic stress disorder	25	10	m
11	ADHD and poly-substance abuse	35	8	f
12	Major depressive disorder	34	11	f
13	ADHD	40	12	m
14	Major depressive disorder	48	16	m
15	ADHD	19	11	m
Group means (in years) or percentage		39	10.8	73% male

identified sequentially. Diagnoses were based on interview by the contributing neuropsychiatrist and review of charts using DSM-IV criteria. MRI was performed as part of a routine neuropsychiatric evaluation, and scans were reviewed by the contributing neuroradiologist for clinically significant findings. Patients gave informed consent to participate. The study was approved by Investigational Review Boards at T-NEMC, Lemuel Shattuck Hospital, and Suffolk University.

Individuals with a psychotic disorder (primarily schizophrenia), mental retardation, significant atrophy, traumatic brain injury, or organic brain disease and those aged 55 years or older were excluded from the study. Enrolled subjects averaged 39 years of age (mean = 39.0, S.D. = 5.8), had just under 11 years of education (mean = 10.80, S.D. = 2.1), and were 73.3% male (11/15).

2.2. Procedures

Participants were administered three aggression and impulsivity questionnaires within 2 weeks of undergoing head MRI. The questionnaires were the Barratt Impulsivity Scale (BIS; Patton et al., 1995), the Lifetime History of Aggression Scale-Revised (LHA-R; Coccaro et al., 1997), and the Buss-Perry Physical Aggression Subscale (BPAPS; Buss and Perry, 1992). The BIS assesses control of thoughts and behavior (e.g., acts without thinking, makes decisions on the spur of the moment), and includes motor, no-planning, and cognitive subscales. The LHA-R measures history of aggressive and antisocial behaviors, and their consequences. The BPA measures trait aggressiveness, the relatively stable tendency to respond to situations with physical aggression. Descriptive statistics for the aggression and impulsivity psychometrics are presented in Table 2.

2.3. MRI acquisition

Three-dimensional (3D) magnetic resonance images were acquired using a 1.5 T superconducting magnet (Siemens, Iselin, NJ). T1 and T2 weighted axial images were acquired with the following parameters: echo time TE1 = 20 ms, TE2 = 80 ms; repetition time (TR) = 2230 ms; flip angle = 65°; field of view = 230 mm; slice thickness = 5 mm, no gaps; matrix = 256 × 256; acquisition time = 3 min. Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) images were acquired in the coronal plane as follows: slice thickness = 1–1.5 mm, matrix = 256 × 256, TR = 11.1 ms, TE = 4.3 ms, FOV = 25 cm, acquisition time = 6 min.

2.4. Image processing

Medx version 3.4.2 visualization and analysis software was used to process MRI data (Medx Users' Guide,

Table 2
Descriptive psychometrics and biometrics

Test name	Group mean	S.D.	Range	Normal mean	S.D.
Barratt Impulsivity Scale (total)	67	13.80	43–87	63.82	10.2
BIS motor subscale	23	5.06	17–34		
BIS no-planning subscale	24.53	7.83	6–35		
BIS cognitive subscale	20.20	3.69	13–26		
Lifetime History of Aggression Scale-Revised	30.27	12.60	8–47	4.9	4.9
Buss-Perry Physical Aggression Subscale	29.27	9.39	10–40	24.3	7.7
Left OFC gray matter (cc)	13.75	1.63	11.19 to 16.77	14.32	2.1
Right OFC gray matter	13.54	1.86	10.63 to 17.08	14.23	1.8
Total OFC	27.29	3.31	21.82–32.31		
OFC asymmetry	−.21	1.12	−1.44 to 2.59		
Whole brain volume	1340	90	1200 to 1500		

2002). The region of interest (orbitofrontal cortex) was derived based on the MRI-based frontal cortex parcellation method of Crespo-Facorro et al. (1999) supplemented by brain atlas referencing (Duvernoy, 1991). The T1-weighted axial images underwent Medx automated transformation into Montreal Neurological Institute (MNI) space (Spatial Normalization with SPM). The spatially normalized images then underwent Medx automated tissue segmentation into gray matter, white matter, cerebrospinal fluid (CSF), skull/membrane compartments, and 'combined' images (Tissue Segmentation with SPM).

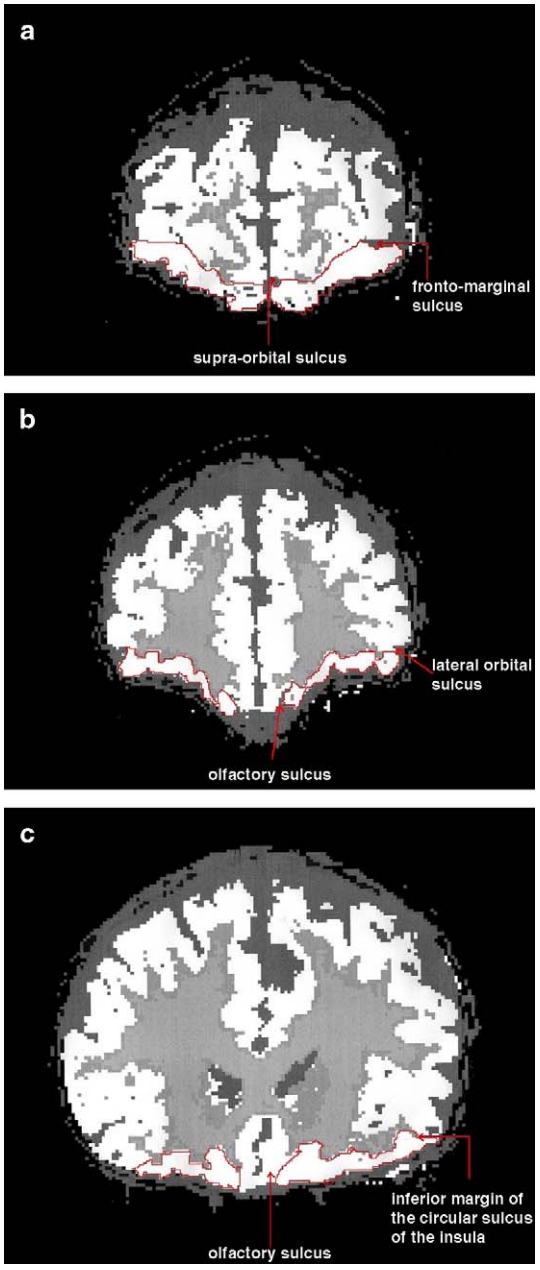

Fig. 1. MNI three-dimensional coordinates for the OFC tracing protocol (all coordinates are for a left hemisphere tracing). (a) Anterior OFC tracing: −1, −19, 63 (medial superior point); −40, −4, 63 (lateral superior point). (b) Mid-OFC tracing: −10, −21, 53 (medial superior point); −46, −10, 53 (lateral superior point). (c) Posterior OFC tracing: −9, −17, 29 (medial superior point); −51, −14, 29 (lateral superior point).

2.5. ROI tracing protocol

The gray matter of the orbitofrontal cortex (OFC) was traced in the coronal plane on the tissue segmented images. Based on the protocol of Crespo-Facorro et al. (2002) the lateral boundary of the OFC was the frontomarginal sulcus anteriorly (see Fig. 1a), the lateral orbital sulcus intermediately (see Fig. 1b), and the inferior margin of the circular sulcus of the insula posteriorly (see Fig. 1c). The medial boundary of the OFC was defined by the supraorbital sulcus on the medial wall on anterior slices (see Fig. 1a), and on mid-to-posterior slices the olfactory sulcus on the ventromedial surface (see Fig. 1b and c). Three-dimensional coordinates in MNI space are provided for the medial superior and lateral superior points of the tracing protocols depicted in Fig. 1a–c.

First, tracing templates were reviewed and approved by the contributing neuroradiologist and neuropsychiatrist, and were available as a visual reference to guide tracing. Second, two independent raters were trained to trace the OFC. Inter-rater reliability was high for both the left and right OFC ($r=0.936$ left OFC; $r=0.937$ right OFC, $P=0.00$) for the first 10 protocols. One of the two trained tracers then proceeded to trace the entire sample. The OFC GM volumes are only slightly lower, by 1/2 to 1 cm^3, than previously published values (Crespo-Facorro et al., 1999).

Whole brain volume (WBV) was calculated on the T2-weighted images based upon the Blatter et al. (1995) method (see also Table 2) for use in partial correlation analysis.

2.6. Statistical analysis

Partial correlation coefficients were calculated between OFC volume measurements and psychometrics controlling for WBV. A probability level of 0.05 was set as the criterion for statistical significance. To address the effects of heterogeneity of psychiatric disorder, the sample was split into subjects with affective disorder ($n=8$) and without affective disorder ($n=7$) for a post hoc analysis.

3. Results

Correlation coefficients were calculated for the two aggression and total and subscale impulsivity psychometrics with the brain indices. It was hypothesized that OFC gray matter would be negatively correlated with aggression and impulsivity. Partial support for the hypotheses was found with aggression, while the direction of association with impulsivity measures was opposite to that predicted. Subjects were subsequently divided into those with and without affective disturbance (see Table 3) to assess the impact of heterogeneity of disorder.

3.1. Aggression measures

Left and right OFC volumes were not significantly associated with aggression psychometrics. However, OFC gray matter asymmetry showed a significant positive correlation correlated with LHA-R ($r=0.63$, $P<0.05$), a measure of frequency of aggressive behavior, but not with BPAPS, a measure of the stable trait of physical aggression. In other words, the larger right OFC gray matter volume was in relation to the left (asymmetry), the higher the LHA-R score.

Table 3
Correlation of aggression and impulsivity psychometrics for those with ($n=8$) and without affective disorder ($n=7$) controlling for whole brain volume

	BPAPS	LHA-R	BIS	BIS-Im	BIS-Inp	BIS-Ic
Affective disorder						
R OFC (cc)	−0.17	−0.03	0.51	0.44	0.43	0.51
L OFC (cc)	−0.66	−0.53	0.63	0.68	0.43	0.56
Total OFC	−0.44	−0.29	0.60	0.58	0.45	0.56
R OFC−L OFC (cc)	0.81*	0.81*	−0.22	−0.42	−0.03	−0.11
Non-affective disorder						
R OFC (cc)	−0.60	−0.05	0.61	0.70	0.73	0.54
L OFC (cc)	−0.54	−0.46	0.68	0.77	0.83*	0.08
Total OFC	−0.64	−0.35	0.74	0.84*	0.90**	0.29
R OFC−L OFC (cc)	−0.35	0.50	−0.34	−0.38	−0.42	0.31

OFC=orbitofrontal cortex volume (R=right, L=left); Total OFC=R OFC+L OFC volume; WB=whole brain volume; R OFC−L OFC=Measure of asymmetry; BPAPS=Buss-Perry Aggression-Physical Aggression Subscale Questionnaire; LHA-R=Lifetime History of Aggression-Revised Questionnaire; BIS=Barratt Impulsivity Scale; BIS-Im=Barratt Impulsivity Motor subscale; BIS-Inp=Barratt Impulsivity Non-planning subscale and BIS-Ic=Barratt Impulsivity Cognitive subscale.
*$P\leq0.05$, two-tailed. **$P\leq0.01$, two-tailed.

3.2. Impulsivity measures

Motor impulsivity was positively and significantly associated with left ($r=0.74$, $P<0.01$), right ($r=0.54$, $P<0.05$), and total OFC gray matter volume ($r=0.67$, $P<0.01$); other BIS subscales were not significantly associated with OFC volume. Asymmetry and impulsivity were unrelated.

3.3. Psychiatric groupings (see Table 3)

3.3.1. Affective disorder

A significant association was only found between OFC asymmetry and aggression. Specifically, greater right relative to left OFC volume showed a positive association with the LHA-R and the BPAPS.

3.3.2. Non-affective disorder

A significant association was found between the OFC and impulsivity. In particular, there was a positive association between total OFC volume and motor impulsivity, as well as between left and total OFC volume and the no-planning subscale of the BIS.

It is noted that with the small sample size outliers could affect correlational analysis; however, there is a systematic and broad-based (linear) association between variables. Furthermore, the small size makes it hard to pick up any effect but a large one, and that with greater sampling more robust associations between the ROI and the psychometrics could have emerged.

4. Discussion

The present study found partial confirmation of hypotheses as well as some counter intuitive but potentially important findings. In a heterogeneous sample of non-psychotic psychiatric patients' self-report of the frequency of aggressive and anti social behavior and its consequences, the LHA-R was significantly and positively associated with OFC asymmetry, such that the smaller the left OFC in relation to the right, the greater the aggressive behavior. Furthermore, a specific type of impulsivity, motor impulsivity (from the BIS), was significantly and positively associated with left, right and total OFC volume. The direction of the relationship was opposite to that predicted; however, the finding is intriguing and broadly supportive of the OFC's contribution to impulsive behavior.

The heterogeneity of the sample appeared to be a contributing factor and one worthy of further attention. Disaggregation of the sample by diagnostic category revealed important distinctions. First, aggressive behav-

ior and impulsivity show differing patterns of organization within the orbitofrontal cortex. Among a sub-group of *affective disorder patients*, a robust association of aggression, measured both as a trait (BPAPS) and by behavioral frequency (LHA-R), with OFC asymmetry emerged, without an association to impulsivity. The asymmetry finding can be viewed in the context of the negative, though not statistically significant, correlation of left OFC volume and aggression. Among a sub-group of *non-affective disordered patients (having ADHD, ASPD, and alcoholism)*, the total OFC volume was significantly associated with both motor and non-planning aspects of impulsivity, but without association to aggression.

These results advance what is known regarding the neuropsychobiology of aggression and impulsivity when considered within the context of a mentally ill population. They represent, to our knowledge, the first report of a volumetric association of a specific subdivision of the PFC, the OFC, with aggression and impulsivity psychometrics. Prior work with violent offending or psychiatric populations has focused on PFC volume as a whole, rather than its dorsal, medial, or ventral subdivisions, or has relied on activation methods. Within that context, the results are broadly consistent with previous work linking general PFC dysfunction to aggression (Giancola and Zeichner, 1994; Raine et al., 1997; Raine et al., 2000; Soderstrom et al., 2000) and specific OFC dysfunction to aggression (Grafman et al., 1996; Pietrini et al., 2000). It is, of course, not inconsistent with reports linking aggression to other foci as well (Gatzke-Kopp et al., 2001; Tonkonogy, 1991; Soderstrom et al., 2000).

The connection/direction of OFC asymmetry, particularly a reduction in the left in proportion to the right, with aggression among a sub-group of affective disordered patients is of interest and may relate to the recent findings of Dougherty et al. (2004), who observed left VMPFC deactivation among individuals with major depression who were prone to anger attacks. Specific pathophysiology that incorporated the amygdala was also posited. The regional volumetric reduction in structural MRI found in this study is also commensurate with the regional deactivation found in functional imaging studies such as that of Dougherty et al. (2004). Connections may also be found to recent evidence linking the left frontal lobe to social permission schema type of reasoning but not the right frontal lobe (Goel et al., 2004). Social reasoning is incorporated here as it may be a critical aspect in the pathophysiology of aggression, both in the psychiatric and general population. This raises the possibility of a confluence of factors; including, pathophysiology of the left OFC and/or VMPFC and their amygdaloid connections, mood disturbance, social reasoning, and aggressive behavior problems.

Consideration should also be given to the pathophysiology/neurophysiology of impulsivity in this discussion of non-psychotic psychiatric patients. The positive association between OFC volume and impulsivity suggests the possibility of a dissociation between aggression and impulsivity. Counter intuitively, a positive association of the OFC and motor impulsivity was found, with OFC association to motor and non-planning aspects of impulsivity in a sub-group of non-affective disorder patients. The possibility of a dissociation of aggression and impulsivity may be weighed here as well. The OFC/VMPFC may play a regulatory role in aggression, as evidenced by the presence of heightened aggressive tendencies when left OFC volume is reduced in comparison to right OFC volume. In regard to impulsivity, the OFC/VMPFC well play a generative role, as evidenced by the association of motor and non-planning impulsivity to greater OFC volume (particularly in non-affective disorder patients). Aron et al. (2004) posit the right IFC, and lesions in that area, are critical to disinhibition, and for the present purposes disinhibition and impulsivity may be considered similar functions. Within a neural network framework of impulsivity, a role for impulse generation may be localized to the OFC, with impulse regulation localized to the IFC (R>L), by way of critical U-shaped fiber linkages between the two regions.

In considering these findings, the quasi-experimental clinical study design must be considered. Level of aggression and impulsivity were not directly manipulated in this study through random assignment. Therefore, it is possible that related variables, such as gender, extent of substance abuse, and variations in the degree of high risk lifestyle, may be influencing the relationship of OFC volume to the aggression and impulsivity characteristics. Limited sample size precludes multi-factorial modeling within this report; however, the utility of such an approach in the future seems clear. These findings highlight the importance of considering the reciprocal or complex relation of type of psychopathology, foci of neurophysiologic dysfunction, and type of behavioral issue, be it aggression, impulsivity, or other relevant phenomena.

It is also worth considering our study outcome in the context of other theoretical work on the neuropsychobiology of aggression. Consistency can be found with Giancola's (1995) notion of the OFC as a pathway to aggression via emotional dysregulation. However, Brower and Price's proposal of an OFC pathway to

impulsive aggression may need to be seen in the context of a PFC system in which the OFC and IFC play reciprocal roles. It is also interesting to consider the view of Davidson et al. (2000) view that the OFC may provide a pathway to aggression via a low threshold for the activation of negative affect. Applying the valence hypothesis of affect, i.e., left hemisphere dominance in the expression of positive affect and right hemisphere dominance for negative affect, fits well with the present asymmetry finding.

Systematic exploration of the neuropsychobiology of impulsivity, incorporating inferolateral and dorsal aspects of the PFC, with continued emphasis on the facets of impulsivity is warranted. Laterality may be particularly important in the neurobiology of aggression and impulsivity. As indicated by Volavka (1999), the role of environmental influences on the neuropsychobiology of aggression (and impulsivity) is extremely important, and contrasting PFC and temporal lobe structures will be critical in delineating the potential contribution of each brain region to this behavior.

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