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A select group of perpetrators of domestic violence: evidence of decreased metabolism in the right hypothalamus and reduced relationships between cortical/subcortical brain structures in position emission tomography

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Abstract

In an earlier study, we reported that some perpetrators of domestic violence evidenced exaggerated fear-related responses to the panicogenic agent sodium lactate. In the current study, we employed positron emission tomography (PET) to investigate our hypothesis that there are differences in the neural structures and/or pathways that mediate and control the expression of fear-induced aggression in perpetrators of domestic violence. Regional cerebral glucose metabolism was measured in eight male perpetrators of domestic violence who fulfilled DSM-III-R criteria for alcohol dependence (DV-ALC), 11 male participants who fulfilled DSM-III-R criteria for alcohol dependence and had no history of interpersonal aggression (ALC) and 10 healthy male participants who did not fulfill criteria for any DSM-III-R axis I diagnosis and had no history of interpersonal aggression (HCS). DV-ALC had a significantly lower mean glucose uptake in the right hypothalamus compared to ALC and HCS. Correlations were performed between measures of glucose utilization in the brain structures involved in fear-induced aggression. The comparison of DV-ALC to HCS and to ALC differed in six and seven comparisons, respectively, involving various cortical and subcortical structures. HCS and ALC differed between the left thalamus and the left posterior orbitofrontal cortex. These PET findings show that some perpetrators of domestic violence differ from control participants in showing lower metabolism in the right hypothalamus and decreased correlations between cortical and subcortical brain structures. A possible psychological covariate of these changes in regional activity might be fear-induced aggression, but this hypothesis should be examined in larger study groups that undergo provocation during imaging.

Keywords: Amygdala; Fear-induced aggression; Fight or flight; Alcoholism

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1. Introduction

Spouses/significant others frequently report that perpetrators of domestic violence display a number of intimidating behaviors (i.e. loud voice, facial grimacing, imposing stance, and physical aggression) intermittently throughout the course of their relationship. According to some perpetrators, these behaviors are not premeditated and usually occur in response to a 'look' or a 'statement' by the spouse/significant other that the perpetrator perceives to be a 'threat.' These perpetrators of domestic violence report that their reaction to this threat is accompanied by an escalating sense of anxiety/fear, autonomic arousal (e.g. palpitations, increased breathing, and nervousness) and a compelling need to 'defend themselves' (Bitler et al., 1994; George et al., 2000).

Conceptually, the above constellation of symptoms and behaviors can be subdivided into 'assessment' and 'response' components. The assessment component is an apparent hypersensitivity to environmental stimuli that is associated with an escalating sense of anxiety/fear. This component is consistent with the results of our previous research showing that a select group of perpetrators of domestic violence, compared with healthy controls, have exaggerated fear-related responses (i.e. fear and panic) to the anxiogenic agent sodium lactate (George et al., 2000). The response component is characterized by a compelling need for the perpetrators to 'defend themselves' and typically leads to verbal and/or physical aggression. The perpetrators' perceived need to defend themselves typically occurs independent of an actual 'physical' threat posed by their spouse/significant other. The concept of fear being associated with aggression is well documented in the animal literature (Siegel et al., 1999; Weinshenker and Siegel, 2002) and is also consistent with the results of our previous sodium lactate study showing that perpetrators of domestic violence experience not only fear and panic, but also rage in response to sodium lactate (George et al., 2000).

The mechanism whereby fear induces aggression involves a complex set of interactions between the environment and various structures in the central nervous system (e.g. the thalamus, hypothalamus, amygdala, orbitofrontal cortex, anterior cingulate, caudate, putamen and nucleus accumbens). External stimuli, which serve to alert the animal to threat/danger, are received by the thalamus (Armony and LeDoux, 1997). From the thalamus, this information is transmitted to both the amygdala and the cortex, which serve to evaluate the nature of the stimulus for an appropriate response (LeDoux, 1994; Armony and LeDoux, 1997; LeDoux, 1998).

The thalamic input to the amygdala provides the mechanism whereby an animal can process and evaluate sensory information quickly and respond rapidly to imminent danger (Armony and LeDoux, 1997). Animal studies indicate that fear conditioning occurs when conditioned and unconditioned stimuli converge in the amygdala (LeDoux et al., 1990; Li et al., 1996). Conditioned fear responses result in the activation of autonomic, behavioral (i.e. freezing) and hormonal (i.e. hypothalamic–pituitary–adrenal axis) responses expressed in the presence of danger (Davis et al., 1994). Humans who have damage to the amygdala are unable to recognize or react to fearful or angry faces and voices (Adolphs et al., 1995; Scott et al., 1997; Adolphs et al., 1998; Morris et al., 1998).

In contrast to the amygdala, the polysynaptic processing of the cortex is slower but results in a more detailed evaluation of environmental stimuli (Li et al., 1996). The medial and orbital areas of the prefrontal cortex provide an affective and cognitive component to sensory information (Bechara et al., 1997; Schoenbaum et al., 1998; Bechara et al., 2000; Elliot et al., 2000; Ongur and Price, 2000). The pathways between the orbital cortex and the amygdala integrate environmental stimuli with fear responses (Perez-Jaranay and Vives, 1991; Schoenbaum et al., 1998). For example, the presence of threatening stimuli causes the amygdala to decrease the firing rate of the medial prefrontal cortex neurons (Garcia et al., 1999) while lesions to the medial prefrontal cortex impair the ability to extinguish conditioned fear responses (Morgan et al., 1993; Morgan and LeDoux, 1995). The evaluation of the fear-eliciting stimulus in the prefrontal cortex results in a 'decision' (Schall, 2001) to respond to the stimulus or to extinguish

the fear-conditioned response (Hariri et al., 2000). Failure to extinguish the conditioned fear response can result in flight or fight behavior mediated by the hypothalamus and brainstem.

Risold et al. (1997) and Swanson (2000) proposed that the hypothalamus and brainstem are sufficient to elicit hard-wired coordinated defensive behaviors (i.e. threatening/aggressive behavior). The associated motor activities (i.e. locomotion) can be activated either reflexively by sensory information or non-reflexively by inputs from the cerebral cortex. The executions of more complex response selections (i.e. hand/arm movements in fighting) require the basal ganglia (Risold et al., 1997).

The basal ganglia have been theorized to perform response selections from a repertoire of learned behavioral responses (Berns and Sejnowski, 1996). Bechara et al. (2000) proposed that the ventromedial sector of the orbitofrontal cortex mediates the emotional processing of events for inhibitory constraint on response selection. Graybiel (1997, 1998) proposed that the basal ganglia control the execution of the selected response through the use of thalamocortical loops and brainstem networks. The basal ganglia control the thalamocortical loops and brainstem motor networks by exerting tonic inhibition and removing the inhibition from the appropriate selected action sequence (Parent and Hazrati, 1995; Middleton and Strick, 2000a,b). The motor, dorsolateral prefrontal, occulomotor, lateral orbitofrontal and limbic loops are also involved in the decision-making process (Mega and Cummings, 1994). The action selection can be executed in either an automatic or attended mode (Jueptner et al., 1997a,b). Graybiel (1997, 1998) proposed that the learned responses consist of motor or cognitive elements organized into 'chunks' of behavior for efficient execution.

In order to disengage from automatic processing in the thalamocortical loops and switch to an attended action, the anterior cingulate cortex must be activated (Carter et al., 1995; Berns et al., 1997; Carter et al., 2000; MacDonald et al., 2000; Paus, 2001). This activation can be produced by attention–demanding stimuli (e.g. pain, threat). The 'affect' region of the anterior cingulate cortex modulates autonomic activity, internal emotional responses and the assignment of emotional valence while the 'cognitive' region is involved in response selection associated with skeletomotor activity (Devinsky et al., 1995). The anterior cingulate cortex receives projections from the amygdala, and is important for the voluntary initiation or inhibition of motor action (Paus, 2001).

The above-described neurocircuitry indicates that there are important connections between the cortical processing of sensory information and subcortical structures that are known to mediate fear-induced aggression. Bard (1928) reported that animals are more likely to respond to environmental stimuli with 'defensive rage' following cortical ablation. An increase in fear reactivity in response to fear conditioning has also been shown in animals with lesions to the dorsal portion of the medial prefrontal cortex (Morgan et al., 1993). Humans who have traumatic or neoplastic lesions involving the orbital and ventromedial prefrontal cortex have an increased likelihood of exhibiting behavioral disinhibition and aggression (LaPierre et al., 1995; Grafman et al., 1996).

The clinical relevance of the cortical/subcortical neuroconnetctions in the processing of threatening stimuli is further supported by functional studies. In animals, Garcia et al. (1999) showed that the presence of threatening stimuli caused an increase in the firing rate of the neurons in the amygdala with a corresponding decrease in the firing rate of the neurons in the medial prefrontal cortex. The decrease in neuronal activity in the prefrontal cortex did not occur when the amygdala was removed. In humans, Hariri et al. (2000) showed cerebral blood flow (rCBF) to the amygdala in healthy controls increased when they were presented with angry or fearful faces. Cognitive labeling of the angry and fearful faces caused a decrease in rCBF to the amygdala and a simultaneous increase in rCBF to the right prefrontal cortex.

We hypothesize that the inappropriate and exaggerated behavioral responses (e.g. loud voice, facial grimacing, imposing stance and physical aggression) evidenced by some perpetrators of domestic violence in response to a 'look' or 'statement' from their spouse/significant other arise from the failure of the cortex to modulate

the rapid but imprecise evaluation of the environmental stimuli performed in the amygdala. We hypothesize that a select group of perpetrators of domestic violence who evidence fear-induced aggression will have either (1) decreased metabolic activity in the frontal regions of the brain [previously seen in human neuroimaging studies involving aggression (Goyer et al., 1994; Raine et al., 1994, 1997, 1998; Volkow et al., 1995; Amen et al., 1996; Pietrini et al., 2000)] or (2) decreased correlations in glucose activity between cortical structures and the amygdala compared with non-violent controls. The decreased correlations would indicate that there are differences in the previously described neuropathways between the amygdala and cortical structures in perpetrators of domestic violence versus non-violent controls. To eliminate the possibility that any observed changes in glucose metabolism are due to structural abnormalities or to psychotic processes, we elected to study perpetrators of domestic violence who had a normal brain MRI scan and a negative history for head trauma, bipolar disorder and schizophrenia.

To test these hypotheses, we administered labeled ^{18}F-2-fluoro-2-deoxyglucose (FDG) during positron emission tomography (PET) to a select group of perpetrators of domestic violence and non-violent controls using a non-threatening challenge paradigm. Our goal was to quantify the metabolic glucose activity present in the previously cited brain regions (thalamus, posterior orbitofrontal cortex, amygdala, basal forebrain, hypothalamus, anterior cingulate cortex, posterior cingulate cortex and caudate) that modulate and/or mediate conditioned fear responses associated with 'fight' behaviors. To assess possible abnormalities in the functional relationship between these structures, we examined correlations in glucose metabolic activity present in those pairs of structures, which are known to have connecting projections. Since there are both ipsilateral and contralateral projections between these structures (Parent and Hazrati, 1995; Risold et al., 1997; An et al., 1998 McDonald, 1998; Ongur et al., 1998; Barbas, 2000; Cavada et al., 2000; Ongur and Price, 2000), we also examined the cross-cortical–striatal correlations.

2. Methods

2.1. Participants

The majority of the perpetrators of domestic violence were recruited through newspaper advertisements (Do You Ever Lose Control?). Non-violent alcoholics were recruited from the clinical program of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institutes of Health (NIH) volunteer office. Participants underwent extensive clinical and physical examinations to ensure that they were in good health. Participants with a history of seizures, head trauma (defined as a period of unconsciousness exceeding 1 h) or medical conditions requiring chronic medications were excluded from participation. All participants had a negative urine screen for illicit drugs. Prior to being studied, participants with a history of alcohol and/or drug abuse were abstinent for at least 3 weeks while other subjects abstained from alcohol for at least 72 h. All participants were medication free for at least 3 weeks prior to the study. Following the abstinence period, the perpetrators of domestic violence had an electroencephalogram (EEG) and MRI of the brain to rule out central nervous system pathology that could contribute to violent behavior. DSM-III-R psychiatric diagnoses were derived using the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al., 1992) with additional alcohol consumption information obtained from the Michigan Alcohol Screening Test (MAST) (Selzer, 1971; Skinner and Sheu, 1982), both of which were administered by a social worker with extensive training in interviewing. Participants with a DSM-III-R diagnosis of either bipolar illness or schizophrenia were excluded.

Participants were classified into three groups. The first group consisted of eight male perpetrators of domestic violence who fulfilled DSM-III-R criteria for alcohol dependence (DV-ALC). The second group consisted of 11 male participants who fulfilled DSM-III-R criteria for alcohol dependence and who had no history of interpersonal aggression (ALC). The third group was a group of healthy comparison subjects (HCS) that consisted of 10 male participants who had no

history of alcohol abuse, alcohol dependence or interpersonal aggression and did not fulfill criteria for any DSM-III-R axis I diagnosis. Spouses/significant others or family members were contacted to verify the presence or absence of physical aggression.

The DV-ALC group consisted of men from a broad range of socioeconomic backgrounds ranging from executives to unemployed individuals. Only those participants who had a history of inflicting repeated acts of significant physical violence (e.g. hitting/punching, aggressive pushing/shoving, choking or using a weapon) toward a spouse/significant other were included. These acts of violence were not premeditated and were typically associated with a constellation of symptoms (e.g. palpitations, increased respiratory rate, tremor, sense of losing control, and feelings of fear and/or being trapped). Following the act of violence, the DV-ALC often reported a sense of remorse for their aggressive behaviors. At least some of the acts of domestic violence occurred when the DV-ALC were not under the influence of alcohol. All of the DV-ALC participated in other domestic violence-related protocols in our laboratory. All of the ALC and nine HCS also participated in these studies. Participants were assessed for age, anxiety [Spielberger Trait Anxiety Inventory (Spielberger et al., 1970)], depression [Hamilton Depression Rating Scale (Hamilton, 1976)] and aggression [Brown-Goodwin Lifetime Aggression Scale (Brown et al., 1979)].

The NIAAA Institutional Review Board approved the study. After a complete description of the study to the participants, written informed consent was obtained.

2.2. Imaging methods

Regional cerebral metabolic rate of glucose uptake (rCMRglc) was measured using FDG PET, as has been previously described (Andreason et al., 1992, 1993, 1994). Participants were scanned 2–3 h after a light meal. Intravenous (IV) and arterial lines were placed for tracer administration and serial blood sampling while participants reclined on the scanner table. Their heads were immobilized with a thermoplastic mask. After aligning the PET camera to the canthomeatal line, a 7.5-min transmission scan was performed to implement attenuation correction. Participants' eyes were covered and earphones were placed on the participants' head. Five microcuries (mCi) of ^{18}FDG were administered intravenously over 60 s. To insure that all participants were in a similar cognitive state during brain uptake of ^{18}FDG, participants performed a simple, auditory continuous performance task (CPT) (Cohen et al., 1992) during the 30 min following ^{18}FDG administration. The task consisted of pressing a button in response to the higher pitched of two tones while ignoring the lower pitched tone. At the end of this 30-min period, the headphones were removed and two scans of 15 slices each were acquired over the next 30 min. Serial blood sampling was performed so that a time–activity curve could be constructed, and to verify that plasma glucose was stable. The conversion of image voxel values from mCi/cc to mg-glucose min^{-1} 100 g^{-1} tissue was performed using previously described methods (Jones et al., 1982; Mazziotta and Phelps, 1986; Brooks et al., 1987; Sokoloff et al., 1977). Scanning was done on a Scanditronix PC2048-15B tomograph with in-plane resolution of 5.2 mm (FWHM) and axial resolution (slice thickness) of 6 mm at the center of the field of view. The voxel dimensions were $2\times2\times3.25$ mm.

2.2.1. PET image registration and analysis

The T_1-weighted MRI scan (consisting of a $256\times256\times124$ matrix of $1\times1\times2$ mm voxels) of each participant was co-registered to its corresponding PET volume (consisting of a $128\times128\times30$ matrix of $2\times2\times3.25$ mm voxels) using a modified surface matching algorithm (Besel and McKay, 1992). This algorithm provides three-dimensional affine transformation parameters to spatially matched surfaces from two corresponding objects. Regions of interest (ROIs) were manually drawn around each desired structure on MR images. The average glucose count within each structure (i.e. ROI) was then computed from its corresponding matching PET image. The CMRglc value for each ROI is the mean value of all voxels

within the ROI. These values are absolute CMRglc values. The ROIs are shown in Fig. 1.

2.3. Statistical analysis

Group comparisons were performed with analyses of variance; least significant difference pairwise comparisons were performed on variables for which ANOVAs were significant. Pearson correlations were calculated for each group and pairwise comparisons (Anderson, 1958) were performed among the groups. All tests performed were two-tailed. The level of significance was chosen to be $P<0.05$ in order to have adequate power with the small sample sizes. Consequently, there were no corrections for multiple testing. For each statistical test, the adequacy was determined by examining normal probability plots of model residuals and tests of homogeneity of variance. The results of these tests justified the use of parametric analyses. All of the statistical analyses in this study were performed using the STATISTICA software package, (StatSoft Inc., 1994, 1999).

3. Results

3.1. Results for Table 1

In Table 1 there is a group effect for the Brown-Goodwin Lifetime Aggression Scale with the DV-ALC mean being significantly larger than the ALC and HCS means. There is no group effect for age. There is a significant group effect for the Spielberger Trait Anxiety Inventory where the DV-ALC mean is significantly larger than the ALC and HCS means. There is a significant group effect for the Michigan Alcohol Screening Test with the means for DV-ALC and ALC being significantly larger than the mean for HCS. There is a significant group effect for lifetime drinking with the means of DV-ALC and ALC being significantly larger than the mean of HCS.

There is no significant group effect for total brain activity [$F(2,26)=1.16$, $P=0.33$]. The Spielberger Trait Anxiety Inventory is not significantly correlated (Pearson correlations) with any of the ROIs in each group. Pearson correlations were also examined for the Brown-Goodwin Lifetime Aggression Scale scores and the ROIs for each group. There were no significant correlations for the ALC group. In the HCS group, there was a significant correlation for the right caudate (-0.78, $P=0.02$). In the DV-ALC there were significant correlations with the left thalamus (0.82, $P=0.02$) and the right basal forebrain (0.84, $P=0.02$). Pairwise tests of equal correlations were performed among the three groups for the right caudate, left thalamus and right basal forebrain. The only significant comparisons occurred between the HCS and DV-ALC for left thalamus (-0.68 vs. 0.82, $P=0.01$) and right basal forebrain (-0.53 vs. 0.84, $P=0.02$) where the first correlation is from the HCS and the second correlation is from the DV-ALC.

3.2. Results for Table 2

Table 2 presents the axis I and axis II diagnoses for the ALC and the DV-ALC. It is apparent that the DV-ALC have considerably more psychopathology (especially anxiety disorders) than the ALC.

3.3. Results for Table 3

The ANOVA in Table 3 shows that there is a significant group effect for the right hypothalamus. The DV-ALC group had a significantly lower mean than the HCS and ALC groups.

3.4. Results for Table 4

The correlation comparisons in Table 4 show several significant differences involving the following pairs of variables: left amygdala vs. right posterior orbitofrontal cortex; left amygdala vs. right basal forebrain; left amygdala vs. anterior cingulate cortex; right amygdala vs. left thalamus; left amygdala vs. left thalamus; left amygdala vs. right thalamus; left thalamus vs. left posterior orbitofrontal cortex; left caudate vs. left thalamus; and left caudate vs. right thalamus. The HCS and ALC differed in one comparison: left thalamus vs. left posterior orbitofrontal cortex. The ALC and the DV-ALC differed in seven comparisons: left amygdala vs. right posterior orbitofrontal cortex,

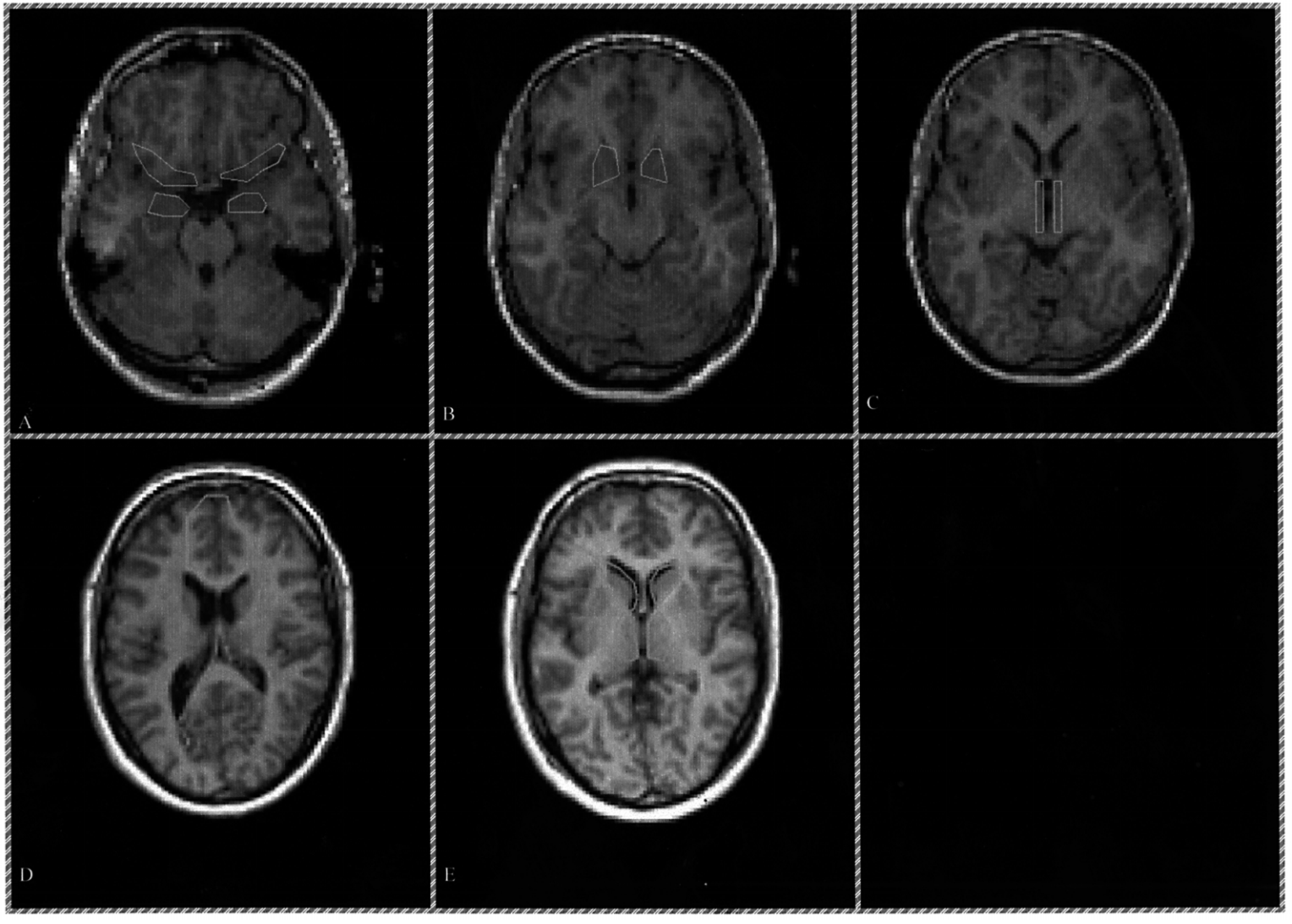

Fig. 1. PET ROI locations in reference to the anterior–posterior commissure (AC-PC). [(a) = posterior orbital cortex (top) and amygdala (bottom): $Z = -13.00$ mm; (b) = basal forebrain, including ventral striatum: $Z = -3.25$ mm; (c) = hypothalamus: $Z = 3.25$ mm; (d) = cingulate cortex: $Z = 6.50$ mm; (e) = caudate (top) and thalamus (bottom): $Z = 6.50$ mm.]

Table 1
Participant characteristics and demographics

	HCS mean ± S.D. $N=10$	ALC mean ± S.D. $N=11$	DV-ALC mean ± S.D. $N=8$	ANOVA d.f.	F	P
Hamilton Depression Rating Scale	2.1 ± 2.3 $N=7$	3.7 ± 2.3 $N=3$	8.2 ± 8.0 $N=6$	2,13	2.2	0.15
Brown-Goodwin[*,a,b]	5.3 ± 5.1 $N=8$	7.6 ± 5.4 $N=10$	25.1 ± 6.8 $N=7$	2,22	26.8	<0.01
Spielberger Trait Anxiety[*,a,b]	29.7 ± 7.4 $N=7$	35.0 ± 8.4 $N=7$	47.4 ± 8.8 $N=7$	2,18	8.5	<0.01
Age (years)	38.1 ± 9.5 $N=9$	39.8 ± 7.2 $N=11$	32.9 ± 6.2 $N=8$	2,25	1.9	0.17
MAST[*,a,c]	0.7 ± 1.2 $N=10$	42.1 ± 18.1 $N=9$	44.3 ± 16.9 $N=8$	2,24	29.3	<0.01
Frequency of drinking in last 180 days (days)[*,a,c]	16.4 ± 22.1 $N=10$	110.7 ± 64.3 $N=9$	95.5 ± 82.1 $N=8$	2,24	6.9	<0.01
Quantity of drinking in last 180 days (g)[*,a,c]	19.3 ± 24.6 $N=10$	197.2 ± 146.7 $N=9$	119.1 ± 82.9 $N=8$	2,24	8.0	<0.01
Heavy drinking (years)[*,a,c]	0.0 ± 0.0 $N=10$	13.1 ± 8.3 $N=9$	8.9 ± 5.8 $N=8$	2,24	13.1	<0.01
Lifetime drinking (kg)[*,a,c]	10.2 ± 16.3 $N=10$	548.7 ± 378.2 $N=9$	378.6 ± 302.6 $N=8$	2,24	9.7	<0.01

[*] Least significant difference pairwise comparison ($P<0.05$).
[a] HCS vs. DV-ALC.
[b] ALC vs. DV-ALC.
[c] HCS vs. ALC.

Table 2
DSM III-R psychiatric diagnoses

AXIS I	ALC $N=10$	DV-ALC $N=8$	AXIS II	ALC $N=10$	DV-ALC $N=8$
Major depression	2	4	Avoident	0	4
Panic attacks	0	3	Dependent	0	4
Agoraphobia	0	2	Obsessive-compulsive	2	4
Social phobia	1	6	Passive-aggressive	0	4
Simple phobia	0	2	Self-defeating	0	4
Obsessive-compulsive disorder	0	1	Paranoid	1	3
Generalized anxiety disorder	0	4	Histrionic	1	1
Organic mood disorder	4	7	Narcissistic	0	4
Organic anxiety disorder	1	4	Borderline	3	7
Posttraumatic stress disorder	2	3	Antisocial	2	5
			NOS	3	6

Table 3
PET regions

	HCS mean ± S.D. $N=10$	ALC mean ± S.D. $N=11$	DV-ALC mean ± S.D. $N=8$	ANOVA		
				d.f.	F	P
Right posterior orbitofrontal cortex	7.55 ± 1.44	7.48 ± 1.21	6.78 ± 1.21	2,26	0.95	0.40
Left posterior orbitofrontal cortex	7.60 ± 1.78	7.55 ± 0.85	7.43 ± 0.72	2,26	0.04	0.96
Right amygdala	5.65 ± 1.06	5.28 ± 0.76	5.02 ± 0.43	2,26	1.39	0.27
Left amygdala	5.73 ± 0.90	5.35 ± 0.94	5.01 ± 0.64	2,26	1.61	0.22
Left basal forebrain	8.82 ± 2.01	8.07 ± 1.55	7.58 ± 1.19	2,26	1.32	0.29
Right basal forebrain	8.63 ± 1.89	7.96 ± 1.65	7.22 ± 1.07	2,26	1.71	0.20
Right hypothalamus[*,a,b]	7.73 ± 1.38	6.96 ± 1.28	5.69 ± 0.86	2,26	6.28	0.01
Left hypothalamus	7.55 ± 1.61	6.68 ± 1.30	5.98 ± 0.77	2,26	3.24	0.06
Anterior cingulate cortex	7.10 ± 1.26	6.82 ± 0.87	6.52 ± 0.68	2,26	0.78	0.47
Posterior cingulate cortex	7.49 ± 1.38	6.98 ± 0.97	6.78 ± 0.86	2,26	1.03	0.37
Left caudate	5.84 ± 0.94	6.47 ± 1.30	6.00 ± 0.75	2,26	1.01	0.38
Right caudate	6.07 ± 1.28	6.36 ± 1.12	6.34 ± 0.86	2,26	0.21	0.81
Left thalamus	7.79 ± 1.90	8.30 ± 1.59	7.48 ± 0.54	2,26	0.71	0.50
Right thalamus	7.74 ± 1.90	8.38 ± 1.43	8.02 ± 0.73	2,26	0.51	0.61

[*] Least significant difference pairwise comparison ($P<0.05$).
[a] HCS vs. DV-ALC.
[b] ALC vs. DV-ALC.

right basal forebrain, anterior cingulate cortex, left thalamus and right thalamus; left thalamus vs. left posterior orbitofrontal cortex; and left caudate vs. right thalamus. The HCS vs. DV-ALC differed in six comparisons: left amygdala vs. right posterior orbitofrontal cortex, anterior cingulate cortex, and left thalamus; right amygdala vs. left thalamus; left caudate vs. left thalamus; and left caudate vs. right thalamus.

4. Discussion

In this study we employed FDG PET to estimate glucose metabolic activity in a number of the brain structures involved in the control and mediation of conditioned fear responses associated with 'fight' behaviors. Our results show that DV-ALC, compared with ALC and HCS, have lower glucose uptake in the hypothalamus as well as decreased correlations among several cortical and subcortical brain structures. The ALC, compared with DV-ALC and HCS, had an abnormally high correlation between left thalamus and left posterior orbitofrontal cortex.

The low hypothalamic glucose metabolic activity found in the DV-ALC compared with both the ALC and HCS suggests that there may be an abnormality in the hypothalamic activity of the DV-ALC. This decreased activity (i.e. relative to the HCS and ALC) does not appear to be related to the effects of alcohol since the ALC group did not exhibit a similar reduction. Since other hypothalamic functions (e.g. consumptive and sexual activities) were normal in all of the participants, we postulate that the low hypothalamic metabolic activity reflects reduced function in specific nuclei such as the dorsal premammillary nucleus, which has been previously shown to be involved in the expression of fear responses (Comoli et al., 2000). The clinical relevance of this finding is substantiated by animal studies showing that the hypothalamus, in conjunction with the periaquaductal gray, is critical in the circuitry that mediates fear-induced aggression (Mos et al., 1982; Sebastian, 1983; Fuchs et al., 1985; Shaikh et al., 1987).

Decreased correlations among various cortical structures (outlined in Table 4) and the amygdala were found in the DV-ALC compared with the ALC and HCS. These reduced correlations involved many of the structures that form the thalamocortical loops (see Section 1) that are

Table 4
Correlations and correlation tests

Variables	Correlations			Significance levels from pairwise tests of equal correlations		
	HCS	ALC	DV-ALC	HCS vs. DV-ALC	ALC vs. DV-ALC	HCS vs. ALC
Right amygdala, right posterior orbitofrontal cortex	0.71*	0.41	−0.28	0.06	0.22	0.40
Left amygdala, right posterior orbitofrontal cortex	0.80*	0.85*	−0.21	0.04†	0.02†	0.77
Right amygdala, left posterior orbitofrontal cortex	0.70*	0.46	0.14	0.24	0.54	0.48
Left amygdala, left posterior orbitofrontal cortex	0.78*	0.88*	0.44	0.34	0.13	0.53
Right amygdala, left basal forebrain	0.69*	0.27	0.41	0.49	0.79	0.29
Left amygdala, left basal forebrain	0.67*	0.54	0.39	0.51	0.74	0.70
Right amygdala, right basal forebrain	0.55	0.21	−0.18	0.19	0.50	0.44
Left amygdala, right basal forebrain	0.58	0.67*	−0.48	0.06	0.03†	0.78
Right amygdala, anterior cingulate cortex	0.78*	0.55	0.22	0.18	0.50	0.42
Left amygdala, anterior cingulate cortex	0.84*	0.91*	−0.03	0.05†	0.02†	0.56
Right amygdala, posterior cingulate cortex	0.77*	0.44	0.58	0.55	0.74	0.30
Left amygdala, posterior cingulate cortex	0.83*	0.85*	0.24	0.13	0.10	0.90
Right amygdala, left caudate	0.70*	0.31	−0.03	0.15	0.55	0.31
Left amygdala, left caudate	0.66*	0.64*	0.49	0.67	0.70	0.54
Right amygdala, right caudate	0.67*	0.62*	0.48	0.63	0.73	0.87
Left amygdala, right caudate	0.56	0.46	0.45	0.80	0.98	0.80
Right amygdala, left thalamus	0.63	0.33	−0.52	0.04†	0.13	0.45
Left amygdala, left thalamus	0.53	0.89*	−0.58	0.05†	<0.01†	0.13
Right amygdala, right thalamus	0.60	0.55	0.18	0.40	0.46	0.89
Left amygdala, right thalamus	0.51	0.80*	−0.39	0.12	0.02†	0.32
Right amygdala, right hypothalamus	0.64*	0.19	0.19	0.35	1.00	0.29
Left amygdala, right hypothalamus	0.64*	0.54	0.10	0.28	0.39	0.77
Right amygdala, left hypothalamus	0.81*	0.57	0.31	0.19	0.57	0.37
Left amygdala, left hypothalamus	0.80*	0.84*	0.61	0.52	0.38	0.82
Right basal forebrain, anterior cingulate cortex	0.63	0.78*	0.84*	0.43	0.76	0.56
Left basal forebrain, anterior cingulate cortex	0.73*	0.67*	0.74*	0.97	0.81	0.82
Right basal forebrain, right hypothalamus	0.77*	0.60	0.18	0.17	0.38	0.54
Left basal forebrain, right hypothalamus	0.67*	0.62*	−0.12	0.13	0.16	0.87
Right basal forebrain, left hypothalamus	0.72*	0.70*	0.15	0.22	0.23	0.94
Left basal forebrain, left hypothalamus	0.86*	0.58	0.70	0.48	0.72	0.24
Right posterior orbitofrontal cortex, right caudate	0.45	0.32	−0.33	0.18	0.26	0.77
Left posterior orbitofrontal cortex, right caudate	0.55	0.58	−0.32	0.13	0.10	0.93
Right posterior orbitofrontal cortex, left caudate	0.37	0.50	0.37	1.00	0.78	0.76
Left posterior orbitofrontal cortex, left caudate	0.31	0.71*	0.47	0.75	0.52	0.29

Table 4 *(Continued)*

Variables	Correlations			Significance levels from pairwise tests of equal correlations		
	HCS	ALC	DV-ALC	HCS vs. DV-ALC	ALC vs. DV-ALC	HCS vs. ALC
Left thalamus, left posterior orbitofrontal cortex	0.13	0.88*	0.05	0.89	0.03†	0.03†
Left thalamus, right posterior orbitofrontal cortex	0.18	0.82*	0.43	0.64	0.24	0.08
Right thalamus, left posterior orbitofrontal cortex	0.29	0.76*	−0.03	0.58	0.09	0.20
Right thalamus, right posterior orbitofrontal cortex	0.29	0.66*	0.35	0.91	0.47	0.35
Right caudate, left thalamus	0.50	0.45	−0.41	0.12	0.13	0.90
Right caudate, right thalamus	0.78*	0.79*	−0.04	0.09	0.07	0.96
Left caudate, left thalamus	0.83*	0.71*	−0.18	0.03†	0.08	0.57
Left caudate, right thalamus	0.86*	0.80*	−0.49	0.01†	0.01†	0.71

† Pairwise test for equal Pearson correlations is significant at 0.05 level.
* Test for zero correlation is significant at 0.05 level.

critical for the control and ultimately for the mediation of fear-induced aggression.

The left amygdala (involved in most of the decreased correlations seen in DV-ALC) is involved in the conscious processing of fearful stimuli, while the right amygdala is involved in the unconscious processing of fearful stimuli (Morris et al., 1998). Animal studies show that the orbitofrontal cortex and the medial prefrontal cortex project to the amygdala, with the amygdala having reciprocal projections to the lateral orbitofrontal cortex and the medial prefrontal cortex (Cavada et al., 2000). The projections from the medial prefrontal cortex to the amygdala involve the binding of presynaptic glutamate to *N*-methyl D-aspartate (NMDA) receptors. These projections are involved in long-term potentiation (LTP) as well as fear extinction (Morgan et al., 1993; LeDoux, 2000). In addition, there is an excitatory connection from the basolateral nucleus of the amygdala to the medial prefrontal cortex (Garcia et al., 1999) which involves pyramidal neurons containing excitatory neurotransmitters (McDonald, 1987) that serve to disengage the cortex in response to overwhelming threat.

The ALC, compared with DV-ALC and HCS, showed an abnormally high correlation between left thalamus and left posterior orbitofrontal cortex. This high correlation could indicate enhanced connections in the lateral orbitofrontal loop, which is theorized to be involved in the addiction process and preservative behaviors (Volkow and Fowler, 2000). Therefore, the increased correlation found in the ALC group may be indicative of an increased susceptibility to conditioned positive reinforcements or cues. The nucleus accumbens and the central nucleus of the amygdala are key components in the circuitry involved in the reinforcing action of ethanol (Koob et al., 1998). The dopamine-containing neurons that project to the nucleus accumbens and the opiate peptide-containing neurons in the central nucleus of the amygdala are activated by ethanol and contribute to the reward system involved in the conditioning process in the ALC (Koob et al., 1998).

The fact that DV-ALC did not manifest a high correlation between the left thalamus and left posterior orbitofrontal cortex suggests that there may be fundamental differences in the biological mechanisms involving alcohol consumption in the DV-ALC and ALC groups. DV-ALC often report that they consume alcohol to decrease their anxiety. (Table 1 shows that Spielberger Trait Anxiety scores are significantly higher in DV-ALC than HCS and ALC.) Gamma-aminobutyric acid-A (GABA-A) receptor-containing neurons in the nucleus accumbens and the central nucleus of the amygdala are activated by ethanol and contribute to decreased anxiety (Volkow and Fowler, 2000; Volkow et al., 1995). The decrease in anxiety may

be an important motivation for ethanol consumption in DV-ALC.

The results from this study are derived from a carefully defined patient population that exhibits fear-induced aggression. Contrary to our first hypothesis, we did not find a difference in glucose metabolism in the frontal regions of the DV-ALC. However, it is possible that we would have found a difference in the frontal regions of the DV-ALC if we had a larger number of participants. The decreased correlations present in the DV-ALC are consistent with our second hypothesis that perpetrators of domestic violence have differences in their neuropathways between the cortex and the amygdala compared with non-violent controls. These differences theoretically compromise the ability of the DV-ALC to modulate the rapid but imprecise evaluation of environmental stimuli performed by the amygdala (see Section 1). The lack of cortical input to the amygdala provides an explanation for the apparent hypersensitivity to environmental stimuli that is manifested by DV-ALC and predisposes the DV-ALC to conditioned fear responses that are manifested as fight behaviors (i.e. need to defend themselves, rage).

Previous imaging studies involving violent individuals have generally found decreased glucose metabolism in the frontal brain regions (Goyer et al., 1994; Raine et al., 1994; Volkow et al., 1995; Amen et al., 1996; Raine et al., 1997). Typically, these studies have not controlled for psychotic diagnoses, central nervous system pathologies or the type of violence. One exception is a study by Raine et al. (1998) where murderers were subcategorized according to the type of violence (i.e. premeditated or defensive/affective). Affective-murderers, compared with comparison subjects, had decreased prefrontal glucose metabolism and a lower right hemisphere prefrontal/subcortical ratio.

In conclusion, this imaging study is the first to examine a carefully defined population of domestic violence offenders. Our results suggest that abnormalities present in the structures/neuropathways of DV-ALC may predispose them to acts of domestic violence. Additional studies, involving a larger number of perpetrators with and without a diagnosis of alcohol dependence, are indicated to explore the affects of fear-related challenge paradigms using functional MRI imaging.

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