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Dorsal/ventral parcellation of the amygdala: Relevance to impulsivity and aggression

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ABSTRACT

Investigations into the specific association of amygdala volume, a critical aspect of the fronto-limbic emotional circuitry, and aggression have produced results broadly consistent with the 'larger is more powerful' doctrine. However, recent reports suggest that the ventral and dorsal aspects of the amygdala play functionally specific roles, respectively, in the activation and control of behavior. Therefore, parceling amygdala volume into dorsal and ventral components might prove productive in testing hypotheses regarding volumetric association to aggression, and impulsivity, a related aspect of self-control. We sought to test this hypothesis in a group of 41 psychiatric patients who received standard magnetic resonance imaging and a psychometric protocol including aggression and impulsivity measures. Whole amygdala volumes were not associated with aggression or impulsivity, but significant correlations were found when dorsal/ventral amygdalae were analyzed separately. Specifically, left and right ventral amygdala volume was positively associated with motor impulsivity, and left dorsal amygdala was negatively associated with aggression. Results are discussed in terms of an activation and control model of brain-behavior relations. Potential relevance to the continuum of amygdala hyper- to hypo-activation and aggression is discussed.

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1. Introduction

Dysfunction of the limbic system, including the amygdala and hippocampus, has been implicated in aggression (Bear, 1991) and in the functional and clinical neuroanatomy of morality (Fumagalli and Priori, 2012). The amygdala and inter-connected cortical areas play an important role in perceiving and responding to threatening stimuli and in regulating aggressive behavior in humans (Goldstein et al., 1996; LeDoux, 2000) and other species (Kluver and Bucy, 1939; Adamec, 1991; Gregg and Siegel, 2001; Saddoris et al., 2005). The structure–function relationship of the amygdala and related structures to the aggressive behavior of antisocial individuals has been extensively reviewed (Raine and Yang, 2006). Among healthy controls the strength of the coupled activity of the amygdala with the orbital frontal cortex or the dorsomedial cortex is related to the degree of attenuation of negative affect generated during emotional re-appraisal (Banks et al., 2007). Siever (2008) reviewed evidence suggesting that aggression is, in part, a result of amygdala activation in the absence of top-down controls, a phenomenon sometimes referred to as dual-brain pathology (Tebartz van Elst et al., 2001).

1.1. The amygdala and dynamic emotional systems.

The amygdala responds selectively to threatening stimuli and plays a role in threat perception (Morris et al., 1996, 1998; Isenberg et al., 1999; Williams et al., 2001). Patients with bilateral amygdalar lesions show deficits in aversive conditioning, recognition of fearful facial expressions, and the ability to produce vocal expressions of fear and anger (LeDoux, 2000). It is not surprising, then, that the amygdala has been shown to project, relative to all cortical regions, most heavily to the medial and orbital frontal regions in macaque monkeys (Amaral and Price, 1984), an area in humans that is critical for executive control of social and emotional processes (Beer et al., 2004). Blair (2007) found an association between the medial frontal cortex and moral decision-making in healthy controls as compared to lateral activation in

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psychopaths. Further, Williams et al. (2001) used simultaneous functional magnetic resonance imaging (fMRI) and skin conductance recording to demonstrate that the amygdala participates in the visceral or emotional experience of threat, as opposed to the "declarative fact" processing of fear engaged by the hippocampus. Phelps et al. (2001) extended this idea with data showing amygdalar activation in response to abstract representations fear and enhanced activity of the left amygdala when the emotional attributes of a stimulus are learned via verbal communication.

1.2. The amygdala and violence

Given the association between the amygdala, fear conditioning, and psychopathy, the question is raised as to the relationship of structural abnormalities in this region and violent behavior. Abnormalities in medial orbital frontal cortex (OFC)–amygdala connections are present in sociopathy, and possibly related to lack of empathy in that population (Blair, 2007). Blair et al. (2006) showed, by patterns of neuropsychological test performance in psychopathy, relative dysfunction of the OFC as opposed to the dorsolateral prefrontal cortex (DLPFC) or anterior cingulate cortex (ACC), implicating the OFC–amygdala social and emotional network (Barbas, 2006). Amygdala atrophy and aggressive behavior have been associated in temporal lobe epilepsy (Tebartz van Elst et al., 2000), as has amygdala volume reduction in 'unsuccessful' psychopaths (Yang et al., 2010). In healthy controls, a 16–18% reduction in whole amygdala volume was found among those who endorsed a greater history of lifetime aggression (Matthies et al., 2012). Moreover, bilateral amydalectomy in patients with intractable aggression led to a reduction in their physiological response to stressful stimuli, and the authors suggested that amygdalectomy restored proper DLPFC (faciliatory) and OFC (inhibitory) balance in autonomic nervous system regulation (Lee et al., 1998). Despite this formulation, there is some recent evidence that OFC contributions to psychopathy are more a function of co-morbid substance use in this population than psychopathy per se (Schiffer et al., 2011).

The above-mentioned findings suggest a complex relationship between amygdala volume and aggression; thus, a more nuanced view of amygdala activation/volume patterns and type of aggression has been emerging. In a study based on Tebartz van Elst's (2001) dual brain pathology, Meyer-Lindenberg et al. (2006) found that left amygdala hyperactivation and ventromedial prefrontal hypoactivation while viewing angry faces were associated with the monoamine oxidase type A (MAOA)-lo allele, which carries an increased risk for impulsive aggression. Meyer-Lindenberg et al. (2006) suggested that the instrumental aggression of psychopathy would be associated with the opposite activation pattern, that is, amygdala hypo-activation (Meyer-Lindenberg et al., 2006). This suggestion coincides with Blair's (2003) proposal of amygdala hypo-activation as a basis for the empathy deficit in psychopaths.

The continuum of amygdala hyper- to hypo-activation can be considered in the context of specific amygdaloid pathways. Perceptions of threatening behaviors are conveyed first to the basolateral (ventral) nuclei of the amygdala via the thalamus or sensory cortex (Davidson et al., 2000; LeDoux, 2000). In this way, the basolateral nuclei act as the sensory gateway to the amygdala and project information to the central nucleus of the amygdala, which subsequently projects to the hypothalamic and brainstem areas that control the expression of fear responses (Feldman and Weidenfeld, 1998). Afferent connections from the OFC to the amygdala are plentiful. Rostral regions of the OFC send projections to the amygdala, including the basal nucleus, but there are comparatively more projections from the OFC to the caudal regions of the amygdala, including all the main subnuclei (i.e. basal, lateral, medial, and central) (Freese and Amaral, 2009). Dysfunction in this circuit causes excessive negative affect (via hyper-activation) or insensitivity to social cues regulating emotion (via hypo-activation). Thus, emotional dysregulation due to amygdala dysfunction has been proposed by several authors to explain a propensity for violence (Weiger and Bear, 1988; Davidson et al., 2000; Blair et al., 2001). Consistent with these models, neuroimaging using positron emission tomography (PET), magnetic resonance imaging (MRI), and single photon emission computed tomography (SPECT) have found anatomical and functional abnormalities of the amygdala and hippocampus in violent offenders (Raine et al., 1997) and psychopaths (Kiehl et al., 2001; Laakso et al., 2001; Soderstrom et al., 2002; Raine et al., 2004; Birbaumer et al., 2005).

Anatomical lesion studies in animals have revealed the existence of amygdala subnuclei with unique connectivity. Choi et al. (2010) demonstrated that loss of the basal or lateral nuclei, but not the central nucleus, had an effect on fear conditioning in rats. Individual or combined lateral and basal amygdala lesions led to deficits in conditional response to footshock avoidance, but there was little effect of central nucleus lesions.

Despite the need for human neuroimaging studies of distinct amygdala subnuclei, the focus on within-amygdaloid regions of interest (ROIs) has been limited. Brown et al. (2006) used fMRI to show during an amygdala-reactivity paradigm (perceptual face-processing task) that trait impulsivity was positively correlated with bilateral ventral amygdala activity, and negatively correlated with right dorsal amygdala activity. The dorsal region of the amygdala, which includes the central nucleus and basal forebrain cell groups, plays an important role in modulating awareness and attention in response to stimuli of uncertain biological relevance. The ventral region of the amygdala consists primarily of the basolateral complex, innervated by sensory input, and has been implicated in the signaling of associative information to guide decision-making. The roles of dorsal and ventral amygdala regions could be described, respectively, as control and activation. Similar to Brown et al. (2006), our research attempted to examine the contribution of amygdaloid regions along a dorsal-ventral axis.

To our knowledge, there have been no previous studies investigating the association between parcellated amygdala volumes determined by high-resolution magnetic resonance imaging (MRI) and the constituents of aggressive behavior in psychiatric patients. LaBar and Warren (2009) reviewed several methodological concerns with neuroimaging the amygdala, but without suggesting a possibility for how to image difficult-to-visualize subnuclei. In the current study, we used anatomic MRI to examine the relationship between psychometric measures of impulsivity, aggression and the volume of the amygdala in a cohort of psychiatric patients. We used the physical and verbal aggression subscale of the Lifetime History of Aggression-Revised (LHA; Coccaro et al., 1997), based on our previous findings (Antonucci et al., 2006; Gansler et al., 2009), and the motor subscale of the Barratt Impulsivity Scale-11 (BIS-11; Patton et al., 1995), which has been found to predict violence in psychiatric patients (Monahan et al., 2000). We considered the psychometric findings within the activation-control framework suggested by Brown et al. (2006).

Based on an activation and control framework, we predicted that a differential relationship would exist between dorsal and ventral regions of the amygdala and impulsivity and aggression. Such dorsal–ventral parcellation does not necessarily conform to nuclei, but it might relate to the activation (dorsal) and control (ventral) regions of the amygdala. Specifically, we hypothesized that (1) whole amygdala volume would not be related to the self-control variables of aggression and impulsivity; (2) dorsal

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