Development and Psychopathology **20** (2008), 1145–1159
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Printed in the United States of America
doi:10.1017/S0954579408000540

The development of antisocial behavior: What can we learn from functional neuroimaging studies?

S. L. CROWE AND R. J. R. BLAIR
National Institute of Mental Health

Abstract

The recent development of low-risk imaging technologies, such as functional magnetic resonance imaging (fMRI), have had a significant impact on the investigation of psychopathologies in children and adolescents. This review considers what we can infer from fMRI work regarding the development of conduct disorder (CD) and oppositional defiant disorder (ODD). We make two central assumptions that are grounded in the empirical literature. First, the diagnoses of CD and ODD identify individuals with heterogeneous pathologies; that is, different developmental pathologies can receive a CDD or ODD diagnosis. This is indicated by the comorbidities associated with CD/ODD, some of which appear to be mutually exclusive at the biological level (e.g., posttraumatic stress disorder [PTSD] and psychopathic tendencies). Second, two populations of antisocial individuals can be identified: those that show an increased risk for only reactive aggression and those that show an increased risk for both reactive and instrumental aggression. We review the fMRI data indicating that particular comorbidities of CD/ODD (i.e., mood and anxiety conditions such as childhood bipolar disorder and PTSD) are associated with either increased responsiveness of neural regions implicated in the basic response to threat (e.g., the amygdala) or decreased responsiveness in regions of frontal cortex (e.g., ventromedial frontal cortex) that are implicated in the regulation of the basic threat response. We suggest why such pathology would increase the risk for reactive aggression and, in turn, lead to the association with a CD/ODD diagnosis. We also review the literature on psychopathic tendencies, a condition where the individual is at significantly elevated risk for both reactive and instrumental aggression. We show that in individuals with psychopathic tendencies, the functioning of the amygdala in stimulus-reinforcement learning and of the ventromedial frontal cortex in the representation of reinforcement expectancies is impaired. We suggest why such pathology would increase the risk for reactive and instrumental aggression and thus also lead to the association with a CD/ODD diagnosis.

The availability of functional imaging methodologies occurred relatively recently. Although the earliest techniques (e.g., positron emission tomography [PET]) were not suitable for child and adolescent populations because they rely on radioactive isotopes, more recent methodologies, such as functional magnetic resonance imaging (fMRI), can be used with younger participants without major risk. Of course, the field remains in its infancy, and when writing this review, we have had to rely on a variety of studies with adult populations and infer results that we anticipate with child and adolescent samples. However, it is a time of considerable and rapid advance, and thus, the gaps in our knowledge base will likely soon be filled.

The overarching goal of this review is to help understand the neurocognitive impairment(s) that increase the risk for antisocial behavior and thus may incur the *Diagnostic and Statistical Manual for Mental Disorders* (*DSM*; American Psychiatric Association, 1994) psychiatric diagnoses of oppositional defiant disorder

This research was supported by the Intramural Research Program of the NIH NIMH.

Address correspondence and reprint requests to: James Blair, Mood & Anxiety Program, National Institute of Mental Health, National Institutes of Health, 15 k North Drive, Bethesda, MD 20892; E-mail: blairj@intra.nimh.nih.gov.

https://doi.org/10.1017/S0954579408000540 Published online by Cambridge University Press

(ODD) and conduct disorder (CD). The persistent feature of ODD is a pattern of persistently negativistic, hostile, defiant, provocative, and disruptive behavior, which is clearly outside the normal range of behavior for a child of the same age in the same sociocultural context. There is frequently low frustration tolerance. The persistent feature of CD is behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of, for example, aggression, property destruction or theft. These diagnoses are partly age dependent. ODD is usually diagnosed before the age of 9–10 years. CD is usually diagnosed after the age of 9 years. Neither can be diagnosed after the age of 18 years when a diagnosis of antisocial personality disorder (APD) may be warranted.

Although not necessarily the consensus view, many authors consider individuals meeting the criteria of CD and ODD to be heterogeneous with respect to the pathology causing their disorder (Blair, Mitchell, & Blair, 2005; Frick & White, 2008; Steiner & Remsing, 2007). This heterogeneity in causal pathology is arguably reflected in the extent of comorbidity of CD and ODD with other disorders (in some samples up to 80%; Steiner & Remsing, 2007). Many diagnoses are associated with CD including posttraumatic stress disorder (PTSD), bipolar disorder, attention-deficit/hyperactivity disorder (ADHD), and psychopathic tendencies. Given that many of these disorders are associated with differing pathophysiologies, some of which appear to be mutually exclusive at the biological level (e.g., PTSD is associated with *increased* amygdala responsiveness, whereas psychopathic tendencies are associated with *reduced* amygdala responsiveness), it is plausible that there are different developmental routes to CD/ODD reflecting differing neurobiological bases. Thus, in this paper, we will examine the neuroimaging literature with regard to (a) the potential neurobiological bases of the developmental routes to CD/ODD, (b) why the aforementioned disorders are associated with an increased risk for CD, and (c) how the different forms of CD may be distinguished at the level of the individual.

In providing a selective review of the imaging literature related to antisocial behavior and the development of CD/ODD, we make a central assumption that there is a fundamental distinction between reactive (mean age = 8.4 years; Steiner, Saxena, & Chang, 2003) and instrumental (instrumental or premeditated; cf. Steiner et al., 2003) aggression (cf. Barratt, Stanford, Dowdy, Liebman, & Kent, 1999; Berkowitz, 1993; Crick & Dodge, 1996; Linnoila et al., 1983). Reactive aggression is triggered by a frustrating or threatening event, and involves unplanned, enraged attacks on the object perceived to be the source of the threat/frustration. This aggression type is often accompanied by anger and can be considered "hot." It is important that it is initiated without regard for any potential goal. This is in direct contrast with instrumental aggression, which is *purposeful and goal directed* (e.g., to obtain the victim's possessions). Furthermore, instrumental aggression need not be accompanied by an emotional state, such as anger, and can be considered "cold" (Steiner et al., 2003).

Drawing a distinction between reactive and instrumental aggression is critical for three main reasons. First, considerable amounts of data strongly support the existence of two relatively separable populations of aggressive individuals: individuals who present with mostly reactive aggression and individuals who present with high levels of mostly proactive and some reactive aggression (Barratt et al., 1999; Connor, 2002; Crick & Dodge, 1996; Linnoila et al., 1983).

Second, reactive and instrumental aggression rely on partially separable neural systems. As such, a principled division can be made among individuals who display antisocial behavior according to the form of the antisocial behavior displayed. We will argue below that the pathophysiologies associated with individuals who present with mostly reactive aggression are notably distinct from the pathophysiology associated with individuals who present with high levels of instrumental and reactive aggression.

Third, and similar to the second reason, there are notable differences in the pathophysiologies implicated in those psychiatric conditions associated with an increased risk for only reactive aggression (e.g., PTSD, childhood bipolar disorder, and intermittent explosive disorder

https://doi.org/10.1017/S0954579408000540 Published online by Cambridge University Press

[IED]) as opposed to the pathophysiology associated with psychopathy, where there is an increased risk for instrumental and reactive aggression (Cornell et al., 1996; Frick, Stickle, Dandreaux, Farrell, & Kimonis, 2005).

It is critical that a failure to distinguish between populations at risk for reactive versus instrumental and reactive aggression can confound interpretation of experimental results because individuals with very different pathophysiologies are likely to be combined in the same group.

The Neurobiological Basis of Reactive Aggression

The neural systems mediating reactive aggression have been extensively investigated in animal studies. All mammalian species appear to exhibit reactive aggression (Blanchard, Blanchard, Takahashi, & Kelley, 1977; Panksepp, 1998), and it is part of the mammalian gradated response to threat. In work with rodents and using an approaching threat model, the Blanchards demonstrated that low levels of danger from distant threats induce freezing. Higher levels of danger from closer threats induce attempts to escape the immediate environment. Higher levels of danger still, when the threat is very close and escape is impossible, initiate reactive aggression (Blanchard et al., 1977).

Animal work indicates that this progressive response to threat is mediated by a basic threat system that runs from medial amygdaloidal areas downward, largely via the stria terminalis to the medial hypothalamus and from there to the dorsal half of the periaqueductal gray (Gregg & Siegel, 2001; Panksepp, 1998). This system is organized in a hierarchical manner such that aggression evoked by stimulation of the amygdala is dependent on the functional integrity of the medial hypothalamus and periaqueductal gray, but aggression evoked by stimulation of the periaqueductal gray is not dependent on the functional integrity of the amygdala (Gregg & Siegel, 2001; Panksepp, 1998). This amygdala–hypothalamus–periaqueductal gray neural system is thought to mediate reactive aggression in humans also (Blair, 2004a). Furthermore, this system is regulated by higher order structures such as the orbital, medial, and inferior frontal cortices (Blair, 2004a).

Reactive Aggression and CD

The animal data briefly described above suggest two possible pathologies that would increase the risk for reactive aggression. First, the responsiveness of the basic threat system might be exogenously or endogenously elevated; second, the functioning of regulatory regions of frontal cortex might be disrupted. These forms of pathology are, of course, not mutually exclusive. Both could give risk to an individual who is more likely to express reactive aggression.

As noted, CD and ODD are comorbid with a variety of mood and anxiety disorders including PTSD and bipolar disorder (Steiner & Remsing, 2007; Zoccolillo, 1992). Moreover, both PTSD (Silva, Derecho, Leong, Weinstock, & Ferrori, 2001, Zoccolillo, 1992) and childhood bipolar disorder (Danielyan, Pathak, Kowatch, Arszman, & Johns, 2007; Faedda, Baldeseorini, Glavinsky, & Austin, 2004; Leibenluft, Blair, Charney, & Pine, 2003) are associated with an increased risk for reactive aggression. The following section briefly reviews the neuroimaging literature with respect to these disorders and examines whether either or both are associated with increased basic threat circuitry responsiveness and/or decreased frontal regulation of emotional responsiveness.

Increased Basic Threat Responsiveness, PTSD, and Reactive Aggression

PTSD is an anxiety disorder that can occur following exposure to trauma. CD/ODD shows significant comorbidity with PTSD (Dixon, Howie, Starling, & Franzep, 2005; Ruchkin, Schwab-Stone, Koposov, Vermeiren, & Steiner, 2002), and PTSD is associated with an increased risk for reactive aggression (Silva et al., 2001, Zoccolillo, 1992). Moreover, exposure to trauma, including violence in the home and neighborhood, has long been linked with an increased probability of reactive aggression (Frazzetto et al., 2007; Neller, Denney, Pietz, & Thomlinson, 2006).

PTSD is also a particularly interesting disorder from a developmental and translational neuroscience perspective. It develops as a consequence of exposure to stressors, although the mechanisms by which stress triggers the

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development of PTSD in humans remain to be fully elucidated.

Studies in animals provide some insight into the link between stress and/or threat and the development of PTSD; considerable animal data clearly demonstrate that stress and/or threat exposure can cause lasting alterations in behavior, brain chemistry, and neural circuitry. These changes occur after both acute and chronic stressors, and are particularly pernicious developmentally following exposure in juvenile animals (Graham et al., 1999; Nemeroff, 2004). After even a single-exposure to a potentially threatening traumatic event, such as predator scent, animals showing the most extreme responses (e.g., behavioral changes, alterations in the hypothalamus–pituitary–adrenal axis or autonomic nervous system) to the threat appear to retain these changes long term (Cohen, Matar, Richter-Levin, & Zohear, 2006). Similar changes in neurochemistry and the hypothalamus–pituitary–adrenal axis have also been found in nonhuman primates after maternal rejection (Maestripieri, Higley, et al., 2006; Maestripieri, McCormack, et al., 2006), stressful foraging environments (Coplan et al., 1996), and when exposed to an acute stressor (Kraemer, Ebert, Schmidt, & McKinney, 1989). Furthermore, regions of threat–response systems, such as the amygdala, appear to be increased in responsiveness as a result of early exposure to stressors (Blaise, Koranda, Chow, Haines, & Dorward, 2008; Kraszpulski, Dickerson, & Salm, 2006; Sabatini et al., 2007; Salm et al., 2004).

As noted above, PTSD is a developmental consequence of exposure to threat. Consistent with the animal data demonstrating that stress and/or threat exposure increases the responsiveness of the basic threat system, neuroimaging work with adult patients with PTSD have also indicated heightened basic threat responses to threat related material (unfortunately, there have been no neuroimaging studies of children or adolescents with PTSD to our knowledge). Specifically, there have been relative relatively consistent findings of increased amygdala responsiveness in patients with PTSD to personalized traumatic narratives (Shin et al., 2004; Rauch et al., 1996), trauma-related cues (Liberzon et al., 1999, Protopopescu et al., 2005), and fearful facial expressions (Armony, Corbo, Clement, & Brunet, 2005; Bryant et al., 2008; Rauch et al., 2000; Shin et al., 2005; Williams et al., 2006; although see Lanius et al., 2001; Shin et al., 1999). Moreover, a recent voxelwise meta-analysis of 14 of these PET or fMRI studies, all of which focused specifically on processing of negative emotional stimuli (i.e., processing of emotional expressions, trauma-related stimuli or scripts, or emotional words), found greater activation in the amygdala as well as in the insula and midcingulate cortex in PTSD patients than in matched comparison subjects (Etkin & Wager, 2007).

In short, animal work demonstrates that exposure to threat increases the responsiveness of the basic threat circuitry. Work with patients with PTSD, a condition consequent on exposure to threat, also reveals increased responsiveness of the basic threat circuitry (particularly, the amygdala). The suggestion here is that there is an increased risk for reactive aggression in patients with PTSD because of this heightened responsiveness of the basic threat circuitry; a threat stimulus that might elicit freezing in a healthy individual is more likely to elicit reactive aggression in a patient with PTSD because the basic threat system is primed to respond by the earlier trauma.

In this context, it is worth noting that in addition to data indicating trauma associated with PTSD increases the responsiveness of the basic threat systems, PTSD has also been associated with decreased responding within regions of the middle prefrontal cortex (PFC) following presentation of traumatic narratives (Lanius et al., 2001; Shin et al., 2004), trauma-related cues (Bremner et al., 1999), fearful facial expressions (Shin et al., 2005; Williams et al., 2006), and during the performance of emotional Stroop interference tasks (Bremner et al., 2004; Shin et al., 2001; but see Bryant et al., 2005; Shin et al., 1997). Moreover, the recent meta-analysis revealed an apparent hypoactivation in PTSD patients in response to negative emotional stimuli in multiple regions including the ventromedial PFC (vmPFC), rostral anterior cingulate cortex, parahippocampal gyrus, dorsal amygdala and anterior hippocampus, orbitofrontal cortex, dorsomedial PFC, dorsal anterior cingulate cortex, and midcingulate cortex (Etkin & Wager, 2007). Given that these frontal regions may regulate the responsiveness of the

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basic threat circuitry (Blair, 2004a), it is possible that the increased risk for reactive aggression in patients with PTSD reflects a reduction of this frontal regulation.

Frontal Regulatory System Dysfunction and an Increased Risk for Reactive Aggression

Although the amygdala is thought to be relatively complete in its structural and functional maturity by puberty (Machado & Bachevalier, 2003, Yakovlev & Lecours, 1967), PFC continues to undergo structural and developmental changes during adolescence (Blumberg et al., 2004). Work with primates shows significant regression of synaptic varicosities in PFC during adolescence (Bourgeois, Goldman-Rakic, & Rakic, 1994; Lewis, 1997), whereas structural fMRI studies with humans show preadolescent increases, and postadolescent decreases, in cortical gray matter (Giedd, 2004; Giedd. Blumenthal, & Jeffries, 1999). It has been suggested that these changes in PFC structure are associated with greater frontal modulation of emotional responding in the postadolescent period (Blumberg et al., 2004). Following on from this, it is plausible that there are conditions where the appropriate development of regulation over the basic threat system is dysfunctional.

Early neurobiological models of antisocial behavior stressed a role for frontal dysfunction (Pennington & Bennetto, 1993; Raine, 2002). These models, however, were relatively nonspecific with respect to the form of antisocial behavior (they typically did not distinguish reactive and instrumental aggression). Moreover, they frequently failed to specify which regions of frontal cortex are critical for antisociality, although implicitly they favored dorsolateral PFC, a region that does not appear to be integrally involved in the regulation of basic threat systems, and when damaged, is not associated with an increased risk for reactive aggression (Grafman et al., 1996). Nevertheless, these models were informative, and fostered an early neuroimaging literature on aggressive individuals (Critchley et al., 2000; Goyer et al., 1994; Raine et al., 1994; Raine, Buchsbaum, & Lacasse, 1997; Raine, Phil, Stoddard, Bihrle, & Buchsbaum, 1998; Schneider et al., 2000; Soderstrom et al., 2002; Soderstrom, Tullberg, Wikkeslso, Ekholm, & Forsman, 2000; Volkow & Tancredi, 1987; Wong et al., 1997; reviewed by Blair, 2004b). Most of these studies examined mainly reactive populations, with the exception of Raine (1998), who identified 9 reactive and 15 instrumental murderers, and found that relative to comparison individuals, the reactive murderers showed lower prefrontal functioning, whereas the instrumental group did not. Although many of these studies did not differentiate which specific prefrontal regions were dysfunctional, an investigation into the relationship between damage to PFC and aggression suggested that lesions to orbitofrontal and medial (as opposed to dorsolateral) PFC were associated with violence (Grafman et al., 1996). Similarly, Goyer et al. (1994) examined cerebral blood flow using PET under resting conditions in 17 patients with personality disorder (antisocial, borderline, dependent, and narcissistic) and 43 comparison individuals and found that lower normalized cerebral blood flow in lateral orbitofrontal cortex (Broca area [BA] 47) correlated with a history of (mainly reactive) aggression. These studies provided early evidence that dysfunction of higher order cortical structures such as the orbital and medial PFC may contribute to aggression in particular populations, potentially via inappropriate regulation over the basic threat system.

There are several psychiatric conditions that appear to be related to dysfunction in frontal systems involved in the regulation of emotion. Two of these, IED and childhood bipolar disorder, have relatively recently begun to be examined using imaging technologies. Both of these disorders are developmental conditions in that they are thought to first manifest during childhood or adolescence. Furthermore, IED and childhood bipolar disorder are both associated with an increased risk for reactive aggression.

Impaired Frontal Regulation, IED, and Reactive Aggression

IED is categorized as a *DSM-IV* Axis I (American Psychiatric Association, 1994) impulse disorder that manifests as impulsive aggression that is disproportionate to the provocation. It emerges clinically during adolescence (Coccaro, Posternak, & Zimmerman, 2005; Coccaro, Schmidt, Samuels,

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& Nestadt, 2004). Given that by definition IED is characterized by reactive aggression, it is logical to hypothesize that dysfunction in amygdala–prefrontal cortical regions may underlie IED's etiology, and there is some evidence supporting this idea. For example, interictal aggression occurring in people with temporal lobe seizure disorders has been related to IED, and quantitative MRI studies indicate decreases in frontal lobe grey matter (Woermann et al., 2000) and amygdala atrophy (van Elst, Woermann, Lemieux, Thompson, & Trimble, 2000) in patients diagnosed with temporal lobe epilepsy plus IED.

Imaging studies in people suffering from IED are limited. Behavioral data, however, suggest that the integrity of their amygdala–orbital/medial PFC network is compromised (Best, Williams, & Coccaro, 2002), and this appears to be supported by a recent fMRI study. In this study, individuals with IED had a greater blood oxygen level dependent (BOLD) response in the amygdala in response to angry faces compared with healthy control subjects (Coccaro, McCloskey, Fitzgerald, & Phan, 2007). Furthermore, in the IED group, there was a breakdown of the amygdala–orbitofrontal cortex (BA 10 extending to BA 11 m) negative functional connectivity observed in healthy volunteers in response to angry faces. Notably, the BOLD responses to angry faces were correlated with scores on the lifetime history of aggression–aggression subscale ($r = .546$, $p < .02$).

Impaired Frontal Regulation, Childhood Bipolar Disorder, and Reactive Aggression

Notably, IED has been linked to bipolar disorder (McElroy, 1999; McElroy, Soutullo, Beckman, Taylor, & Keck, 1998), and the two disorders symptomatically overlap, although they are currently viewed as categorically different. As with IED, there is mounting evidence that regions involved in threat reactivity, especially the amygdala, may be altered in bipolar disorder. Importantly, amygdala dysfunction appears to be an early feature of the disorder as evidenced by structural, behavioral, and imaging data. Multiple structural imaging studies reported reduced amygdala volume in bipolar adolescents (average age of participants across studies is in the very late teens), a results that has been fairly consistent among studies (Blumberg et al., 2003, 2005; Chen et al., 2004; DelBello, Zimmerman, Mills, Getz, & Strakowski, 2004). Structural studies also point to higher order dysfunction in childhood bipolar disorder, which may contribute to reactive aggression. Differences in PFC morphology, including ventrolateral PFC and anterior cingulate, have been reported in adults with bipolar disorder (Lochhead, Parsey, Oquendo, & Mann, 2004; Lyoo et al., 2004; McIntosh et al., 2004), but such findings have been less consistent in adolescents (mean age = 19.9 years; Adler et al., 2007). This may suggest that ventral PFC abnormalities occur later on in development, potentially resulting in an impairment of cognitive control over threat processing. If this is the case, it would indicate that the developmental trajectory of cognitive control processes over emotional responding differs between individuals with and without bipolar disorder.

Although there are few functional imaging studies investigating emotional processing in bipolar adolescents, there is some evidence that dysfunction in subcortical and prefrontal regions of the brain may occur early in development in this disorder. For example, in response to happy and angry faces, adolescents with bipolar disorder (mean age = 14.9 years) had greater activation than the healthy comparison group in the rostral anterior cingulate, right amygdala, caudate, and thalamocortical loop (Pavuluri, O'Connor, Harral, & Sweeney, 2007). These deficits in subcortical activation during emotional processing appear to extend into adulthood in bipolar disorder (Altshuler et al., 2005). Similar to the structural data for childhood bipolar disorder, bipolar adolescents have also been shown to have altered activity in cortical regions known to be involved in emotional regulation. For example, activation in orbitofrontal and dorsolateral PFC in response to angry faces was lower in bipolar adolescents than that occurring in the healthy comparison group (Pavuluri et al., 2007).

The Neurobiological Basis of Instrumental Aggression

Instrumental aggression is a form of instrumental behavior, that is, a behavior undertaken to achieve a particular goal. In the case of instru-

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mental aggression, an individual uses violence in the expectation that this will allow the individual's goal to be met. When faced with a goal ("obtain $50"), the individual has a range of behavioral options (e.g., "find a job," "mug someone"). Choosing between these choices will be a function first of availability (Can a job/potential victim be found?) and then of action costs (social punishment and the distress of the victims). Thus, an individual might choose an antisocial behavior because they are under social or situational pressure to do so, and in turn, the antisocial acts are simply the most viable options available. In this case, the instrumental aggression/antisocial behavior, whereas perhaps socially undesirable, need not be maladaptive; from the individual's perspective, it may be the only way to achieve their goals. An individual may also choose antisocial behavior because their calculation of the costs related to the actions, empathic responding, or use of this information is deficient. Instrumental aggression/antisocial behavior can thus be considered maladaptive if the decision making that leads to the choice of the action is dysfunctional.

A crucial process for socialization is the ability to form stimulus–reinforcement associations. To learn that hitting another individual is bad, a representation of this action must be associated with an aversive unconditioned stimulus. Considerable literature implicates the role of the amygdala in the formation and processing of stimulus–reinforcement associations (Baxter & Murray, 2002; Everitt, Cardinal, Parkinson, & Robbins, 2003). The aversive unconditioned stimulus that is particularly important for moral socialization is the distress of other individuals such as the expressions of fear and sadness (Blair, 2003). The expressions of fear and sadness serve as social reinforcers; as such, they allow caregivers to teach the societal valence of objects and actions to the developing individual (Blair, 2003). In healthy developing children, actions or objects associated with the sadness and/or fear of others are avoided from an early age (within the second year of life). A considerable body of work attests to the power of facial expressions to transmit valence information in both humans and other primates (Blair, 2003; Klinnert, Emde, Butterfield, & Campos, 1987; Mineka & Cook, 1993). The amygdala is crucially involved in the response to fearful and sad expressions (Adolphs, 2002; Blair, 2003). Moreover, recent fMRI work has shown that the amygdala's response to fearful expressions is modulated by whether there is an object to make the association of the distress of the expression with (Hooker, Germaine, Knight, & d'Esposito, 2006). Specifically, Hooker et al. (2006) demonstrated that healthy adults show significantly greater amygdala activity to individuals displaying fear when looking at a novel object rather than when looking at an empty space. In short, the amygdala shows significantly greater activity when given an opportunity to engage in stimulus–reinforcement learning (stimulus = novel object, reinforcement = fearful expression) than when there is no novel object about which to learn.

Moral socialization by parents and peers helps the developing child appropriately represent the costs of antisocial behavior. An important temperamental variable influencing the ease with which a child can be socialized is fearfulness (Kochanska, 1997; Steiner & Remsing, 2007). We believe that this temperamental variable can be considered to index the functional integrity of the amygdala. The punishment that best achieves moral socialization is the victim's distress; empathy induction, focusing the transgressor's attention on the victim, particularly fosters moral socialization (Eisenberg, 2002; Hoffman, 1994).

The above suggests that pathology interfering with the ease of socialization would increase the risk for instrumental aggression. It is argued that this is what has occurred in the developmental condition of psychopathy (Blair, 2007). Certainly, the relationship between effective parenting techniques (e.g., low levels of corporal punishment, consistency, good monitoring, and high parental involvement) and decreased antisocial behavior that is seen in typically developing children (with low callous-unemotional [CU] traits), does not hold for children who present with the emotional dysfunction associated with psychopathy (mean age = 8.4 years; Oxford, Cavell, & Hughes, 2003; Wootton, Frick, Shelton, & Silverthorn, 1997).

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Impaired Systems for Socialization and Psychopathy

Psychopathy is not currently included in *DSM-IV* (American Psychiatric Association, 1994) and should not be considered synonymous with CD or APD; fewer than 25% of those meeting diagnosis for CD or APD would meet cutoffs for psychopathy (Hare, Glass, & Newman, 2006). Psychopathy has behavioral components (e.g., criminal activity and poor behavioral control), but it also has important affective-interpersonal components (notably, a lack of empathy and guilt; Frick et al., 1994; Harpur & Hare, 1994). It is a developmental disorder (Lynam et al., 2007) where recent work has confirmed the stability of CU traits in particular and the disorder more generally from childhood into adulthood (Lynam, Caspi, Moffitt, Loeber, & Stouthamer-Loeber, 2007, Munoz & Frick, 2007, Obradović, Pardini, Long, & Loeber, 2007). Moreover, CU traits indexed in adolescents have been shown to predict adult measures of psychopathy in early adulthood (Burke, Loeber, & Lahey, 2007, Lynam et al., 2007). In addition, the functional impairments seen in adults with psychopathy (e.g., in responding to emotional expressions, aversive conditioning, passive avoidance learning, reversal learning, extinction) are also seen, with some caveats (see below) in adolescents with psychopathic tendencies (Blair, in press).

There appears to be a strong genetic contribution to the emotion dysfunction that underlies the CU traits. For example, in a recent large study with around 3,500 twin pairs, CU traits were shown to be strongly heritable (67% heritability) at both 7 and 9 years (Blonigen, Hicks, Krueger, Patrick, & Iacono, 2005; Viding, Blair, Moffitt, & Plomin, 2005). However, as yet, the details of this contribution, the molecular genetics, are almost completely unknown. It can be assumed, given the known pathophysiology (see below), that they influence the functional integrity of the amygdala and vmPFC. Moreover, several genes have been identified that do influence the functional integrity of these structures (serotonin transporter *5-HTTLPR*, and monoamine oxidase A *MAOA*; Hariri et al., 2005; Meyer-Lindenberg et al., 2006). However, we do not know whether these genes are implicated in psychopathy.

Social factors influence the manifestation of psychopathy. For example, socioeconomic status (SES) is associated with the emergence of the full syndrome; it is significantly less likely to appear in individuals of higher social status (Silverthorn & Frick, 1999). Reduced SES does not predispose toward reduced emotional and amygdala responsiveness; indeed, as a factor it is unrelated to the emotional component of psychopathy (Hare & Neumann, 2006). However, reduced SES does supply a motive: a lack of finances. Reduced SES increases the risk for antisocial behavior in individuals, including those with psychopathy.

The core deficits seen in psychopathy all relate to the functional role of the amygdala in stimulus–reinforcement learning and in responding to fearful and sad expressions. The impairment of individuals with psychopathy in stimulus–reinforcement association is evidenced by their impairment in aversive conditioning, the augmentation of the startle reflex following the presentation of visual threat primes and passive avoidance learning (Flor, Birbaumer, Hermann, Ziegler, & Patrick, 2002; Levenston, Patrick, Bradley, & Lang, 2000; Newman & Kosson, 1986). Moreover, recent fMRI work has demonstrated that individuals with psychopathy show reduced amygdala responding during aversive conditioning relative to comparison individuals (Birbaumer et al., 2005). Several studies across groups have now demonstrated impairment in the recognition of fearful and, to a lesser extent, sad expressions in individuals with psychopathy (Blair et al., 2001; Dadds et al., 2006; Dolan & Fullam, 2006; but see Kosson, Suchy, Mayer, & Libby, 2002). In addition, fMRI work has indicated that individuals with psychopathic traits show reduced responding to fearful expressions (Gordon, Baird, & End, 2004). Other work has shown that individuals with psychopathy show reduced amygdala responding to emotional words in the context of emotional memory paradigms (Kiehl et al., 2001) and less amygdala differentiation in responding when making cooperation relative to defection choices in a prisoner's dilemma paradigm (Rilling et al., 2007).

The amygdala appears to feed reinforcement information associated with stimuli forward to

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medial orbitofrontal cortex, which then represents this outcome information. The function of this representation of reinforcement information within orbitofrontal cortex is to allow the normalization of competing outcomes so that the value of differing rewards such as apples and oranges can be compared (Montague & Berns, 2002; Padoa-Schioppa & Assad, 2006; Schoenbaum & Roesch, 2005). This reinforcement expectancy information can then be used in decisions as to whether to approach the object or action or not. Given the suggestion made above, that the amygdala's role in stimulus–reinforcement learning is disrupted in psychopathy, it might be expected that individuals with psychopathy will show anomalous medial orbitofrontal cortex activity in the context of tasks that activate the amygdala. This is exactly what is seen. In Kiehl's study of emotional memory, the individuals with psychopathy not only showed reduced amygdala responses to the emotional words but also reduced rostral anterior cingulate cortex/medial orbitofrontal cortex activation (Kiehl et al., 2001). There was also reduced medial orbitofrontal cortex activity in the individuals with psychopathy during aversive conditioning (Birbaumer et al., 2005) as well as less medial orbitofrontal cortex differentiation in responding when making cooperation relative to defection choices in the prisoner's dilemma paradigm (Rilling et al., 2007). Moreover, work has demonstrated reduced functional connectivity between the amygdala and vmPFC in adolescents with psychopathic traits when responding to emotional expressions.

Some recent fMRI work has specifically involved adolescent samples. Sterzer, Stadler, Krebs, Kleinschmidt, and Paustka (2005) reported reduced responding in dorsal anterior cingulate cortex in children with CD (mean age = 12.85 years) to negative images. In addition, following correction for anxiety and depressive symptoms, they also showed less differential responsiveness within the amygdala to negative relative to neutral images in the children with CD (Sterzer et al., 2007). However, these data must be treated with some caution given the very significant groups differences in IQ ($p < .001$). It was interesting that, in a follow-up study with IQ-matched groups and an optimized voxel-based morphometry protocol, these authors observed significant reductions in gray matter volume in bilateral anterior insular cortex and the left amygdala in the children with CD relative to healthy comparison individuals (Sterzer et al., 2007). Moreover, bilateral anterior insular gray matter volume was significantly correlated with self-reported empathy scores in the children with CD.

Three studies have examined children with psychopathic tendencies. Two of these compared responding to fearful and neutral expressions in adolescents with psychopathic tendencies (mean age = 14.5 years) relative to comparison children (E. Viding, personal communication; Marsh et al., 2008). In both of these studies, the children with psychopathic tendencies showed a reduced amygdala response to the fearful expressions relative to the comparison populations. Moreover, the Marsh et al. study also reported reduced functional connectivity between the amygdala and vmPFC in children with psychopathic tendencies relative to comparison children. In addition, in this study, the children with psychopathic tendencies showed reduced amygdala responding to fearful expressions not only relative to healthy developing children but also children with ADHD. This is important because CD/psychopathic tendencies are frequently comorbid with ADHD (e.g., Colledge & Blair, 2001; Taylor, Schachar, Thorley, & Wieselberg, 1986); roughly 50% of the children with psychopathic tendencies in the Marsh et al. study also met criteria for ADHD.

The third study examined reversal learning in children with psychopathic tendencies (mean age = 13.8 years; Finger et al., 2008). In this study, children with psychopathic tendencies and comparison children performed a probabilistic reversal learning paradigm similar to that described by Budhani, Marsh, Pine, and Blair (2007). For this paradigm, the vmPFC showed a reduced BOLD response to punished incorrect reversal phases responses relative to correct responses in healthy adults (Budhani et al., 2007). This was consistent with the suggestion that the vmPFC was responding to the prediction error, the failure to receive the anticipated reward. In the Finger et al. study, the healthy developing comparison children also showed significant reductions in BOLD responses in the vmPFC to punished incorrect reversal responses relative to

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correct responses. In contrast, the children with psychopathic tendencies did not.

The developmental trajectory of these deficits in individuals with psychopathic tendencies remains largely unknown. There is almost no work on the neurocognitive impairments associated with psychopathy in populations less than 10 years of age. The first fMRI studies of adolescent individuals with psychopathic tendencies have only emerged this year (2008). The genetic contribution might suggest an early emergence of the basic pathology, particularly the amygdala dysfunction, given that it is a relatively early maturing structure (Machado & Bachevalier, 2003; Yakovlev & Lecours, 1967). Certainly, the deficits associated with amygdala dysfunction (e.g., in aversive conditioning and passive avoidance learning) appear to be present in adolescent samples (Blair, 2007). However, this has not been empirically confirmed. One difference that does appear between adolescent and adult samples with the disorder is the extent of the pathology, in particular, the deficit in reversal learning, linked to the vmPFC. This deficit is far more marked in adult individuals with psychopathic traits relative to adolescents (Budhani & Blair, 2005; Budhani, Richell, & Blair, 2006). This may indicate a later impact of the genetic contribution or of the amygdala dysfunction itself on the development of the vmPFC. However, again, the critical empirical studies have yet to be conducted.

Conclusions

As noted, there are few fMRI studies of children or adolescents meeting the criteria for ODD/CD. However, there is a slightly larger body of literature examining adult populations, and we have attempted to infer from these data what we anticipate will be seen in future work with child and adolescent populations.

To begin examining the development of antisocial behavior using imaging technologies, we make one major assumption: individuals meeting criteria for ODD and/or CD can be divided into two populations. At the behavioral level, these children can be distinguished by the form of their antisocial behavior. One group displays primarily reactive aggression while the other group is at increased risk for both reactive and instrumental aggression. We believe that the group showing primarily reactive aggression will be those children and adolescents with ODD/CD who are comorbid for mood and anxiety conditions such as PTSD and childhood bipolar disorder. In contrast, we believe that the group showing both reactive and instrumental aggression will include those individuals who show psychopathic tendencies. Certainly, individuals with psychopathic tendencies are at increased risk for reactive and instrumental aggression (Cornell et al., 1996; Frick et al., 2005). Moreover, the dysfunction occurring in psychopathy appears incompatible with that observed in PTSD. For example, psychopathy is associated with decreased amygdala responsiveness, whereas PTSD is associated with increased amygdala responsiveness. Furthermore, it has been suggested that psychopathy is protective regarding the emergence of mood and anxiety disorders (Verona, Patrick, & Joiner, 2001).

Although there have been no fMRI studies attempting to disentangle these two putative populations, it is clear that individuals with the comorbid conditions of PTSD and childhood bipolar disorder show increased BOLD responses within the amygdala and decreased BOLD responses within some regions of frontal cortex. This is consistent with suggestions of increased basic threat circuitry responsiveness and decreased frontal regulatory responsiveness, conditions that should theoretically increase the probability of reactive aggression.

FMRI studies have consistently implicated the amygdala and vmPFC in the pathology of individuals with psychopathic tendencies. Dysfunction in this circuitry may relate to the suggestion that the core impairments occurring in this population result from atypical stimulus–reinforcement learning and the representation of outcome information. Such impairments would, in turn, interfere with moral socialization and decision making. It is quite possible that other neural regions are also involved in the pathology underlying psychopathic tendencies. However, it is currently unclear whether results, indicating differential responses in other regions (e.g., in superior temporal sulcus or dorsal anterior cingulate cortex) reflect specific dysfunction in these regions or instead result from anomalous signaling caused by reduced input from the core regions of the amygdala and vmPFC.

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Clearly, the field is still in its infancy, but progress is rapidly being made. As we have a clearer picture of the pathophysiology or, as we suspect, pathophysiologies associated with ODD and CD, we anticipate an increase in targeted treatment possibilities. Furthermore, understanding the developmental trajectories of different subpopulations of individuals with ODD or CD may improve the ability to target specific neural systems at the appropriate time during development, potentially impacting the subsequent development of comorbid conditions.

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