THE BEHAVIORAL AND NEURAL BASIS OF EMOTIONAL FACE PROCESSING IN ATYPICALLY DEVELOPING CHILDREN AND ADOLESCENTS

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By

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ABSTRACT

The ability to recognize, interpret, and respond appropriately to the affective facial expressions of others is an important component of non-verbal communication; when face-emotion recognition is impaired there can be profound downstream consequences for social competencies such as empathy. This dissertation investigated the behavioral and neurocognitive underpinnings of face-emotion recognition in two developmental disorders—autism spectrum disorders (ASD) and psychopathy—associated with impaired facial affect recognition and dysfunction in empathic behavior. Three studies were conducted: 1) A meta-analysis of explicit face-emotion recognition associated with ASD combined data from 1,545 participants across forty-three studies. The results indicated individuals with ASD have generalized deficits in recognizing facial expressions and that face-emotion recognition abilities develop along a trajectory that differs from typical individuals. 2) Functional magnetic resonance imaging (fMRI) was used to investigate face-emotion recognition in children and adolescents with conduct problems and callous-unemotional traits, a developmental precursor to adult psychopathy. This study found externalizing behaviors were positively associated with amygdala responses to fearful facial expressions and callous-unemotional traits were negatively associated with amygdala responses to fearful facial expressions. Additionally, amygdala responses mediated the relationship between callous-unemotional traits and proactive aggression. 3) In the same sample...
of youths with conduct problems and callous-unemotional traits, voxel-based morphometry was used to investigate how structural brain differences relate to externalizing behaviors and callous-unemotional traits, and found gray matter volume in several regions including the amygdala was positively associated with callous-unemotional traits. Finally, the results of all three studies were discussed in context of empathic deficits, which are also characteristic of ASD and psychopathy.
The research and writing of this thesis
is dedicated to everyone who helped along the way.

Many thanks,
LEAH M. LOZIER
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Chapter I

General Introduction

The movements of expression in the face and body, whatever their origin may have been, are in themselves of much importance to our welfare. They serve as the first means of communication between the mother and her infant; she smiles approval, and thus encourages her child on the right path, or frowns disapproval. We readily perceive sympathy in others by their expression; our sufferings are thus mitigated by and our pleasures increased; and mutual good feeling is thus strengthened. The movements of expression give vividness and energy to our spoken words. They reveal thoughts and intentions of others more truly than do words, which may be falsified...These results follow partly from the intimate relation which exists between almost all the emotions and their outward manifestations; and partly from the direct influence of exertion on the heart, and consequently on the brain. Even the simulation of an emotion tends to arouse it in our minds. –Charles Darwin, The Expression of the Emotions in Man and Animals

Charles Darwin was perhaps the first person to undertake the scientific study of human emotional facial expressions, expounded in his 1872 work, The Expression of the Emotions in Man and Animals. Darwin’s ideas laid the framework for decades of research that has sought to understand human emotional facial expressions. This dissertation will investigate the behavioral and neural basis of face-emotion processing in individuals with autism spectrum disorders and psychopathy and how this relates to the development of empathy.
Darwin, spurred by observations of similar displays of facial affect across human and non-human primates, posited an evolutionary explanation for emotional facial expressions (Darwin, 1998). His account was based on the premise that these expressions were co-opted from facial movements that had evolved for non-communication functions, such as those movements necessary for vision and olfaction (Darwin, 1998; Fridlund, 1991). His argument was directly in contrast to some of his contemporaries, most notably Charles Bell, who believed affective facial expressions were a God-given, uniquely human means of communicating emotion (Fridlund, 1991). Since then, there has been substantial debate as to meaning and utility of displays of facial affect, largely centered around two opposing models—the “emotions view”, expressed in Ekman’s neurocultural model (Ekman, Friesen, & Ellsworth, 1972), and the “behavioral ecology view” proposed by Fridlund (Fridlund, 1994). The “emotions view” posits emotional facial expressions are “readouts” of one’s internal state that result in the display of universal, prototypical expressions associated with discrete emotions (such as happiness and fear) (Ekman, Sorenson, & Friesen, 1969; Ekman et al., 1972). These expressions may have slight variations based on cultural display rules and social norms (Ekman et al., 1987; Elfenbein & Ambady, 2002), but are evolved, innate, and largely reflexive displays of emotion (Ekman, 1993). By contrast, the “behavioral ecology view” purports emotional facial expressions evolved as social displays primarily for communication; they signal what the individual expressing the emotion intends to do, and cue others how to behave in response (Fridlund, 1991; Fridlund, 1994).

Accumulating evidence suggests a more nuanced, integrative approach to understanding emotional facial expressions that integrates both the “emotions view” and the “behavioral ecology view” and acknowledges these expression connote internal states and communicate
social information (Yik & Russell, 1999; Horstmann, 2003; Blair, 2003b). In this vein, emotions are conceptualized as semi-discrete categories that correspond to a specific integral affect state, are associated with prototypical facial displays governed by innate, reflexive muscle movements, and communicate socially-relevant information. Although there is disagreement (Barrett, 2006) as to whether emotions are actually discrete constructs (Posner, Russell, & Peterson, 2005), what constitutes a basic emotion (Ekman & Cordaro, 2011; Frijda & Parrott, 2011; Izard, 2007), and how accurately subjective feelings of emotion correspond to prototypical facial displays (Schützwohl & Reisenzein, 2012), the dominant methodological approach is to employ a categorical framework of facial affect comprised of six basic human emotional facial expressions—anger, disgust, fear, happiness, sadness, and surprise (Ekman et al., 1972)—which will also be used in this dissertation.

The interplay between someone expressing an emotion and another perceiving and recognizing that emotion is the crux of human non-verbal social communication, and the production of these expressions is non-trivial, requiring both cortical and sub-cortical processing (Blair, 2003b). Of particular importance are the frontal cortex and basal ganglia, which have reciprocal connections with one another as well as areas integral for affective processing such as the amygdala (Blair, 2003b). These areas coordinate motor output that activates distinct facial muscles depending on the emotion to be expressed. For instance, anger is expressed by drawing the eyebrows together and downward, tensing the eyelids, and either pressing the lips together or parting them into a square shape (Ekman & Friesen, 2003), and communicates threat and dominance (Marsh, Ambady, & Kleck, 2005; Wilkowski & Meier, 2010). Disgust involves raising the upper lip and wrinkling the nose (Ekman & Friesen, 2003), and signals the presence
of food-related contamination or biological contagions (Rozin & Fallon, 1987) as well as sexual and social transgressions (Hein, Silani, Preuschoff, Batson, & Singer, 2010). Perhaps the most widely studied facial expression is fear, which will be addressed in further detail in subsequent chapters. Characterized by drawn and raised eyebrows, widened eyes, and stretched lips (Ekman & Friesen, 2003), facial expressions of fear are often described as conveying impending threat, danger, or harm (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Fitzgerald, Angstadt, Jelsone, Nathan, & Phan, 2006; Cressey, 2007; LeDoux, 2003; Lang, Davis, & Ohman, 2000) and may elicit approach and empathic concern from the observer (Marsh et al., 2005; Hess, Blairy, & Kleck, 2000).

The communicative functions of these expressions, however, ultimately hinges on the abilities of others to accurately perceive, decode, and recognize these signals. For most individuals, the ability to tell how someone feels just by looking at their face is largely an automatic, unconscious process that belies the enormous complexity and sophistication that underlies face-emotion recognition, which is the culmination of protracted, dynamic, and reciprocal biological-environmental interactions that occur throughout development (Leppanen & Nelson, 2009). Nascent face-emotion recognition is manifest from birth as infants attend to human faces and during the first three months may be able to detect face-like shapes on the basis of high-contrast information (Somerville, Fani, & McClure-Tone, 2011). Within a few months, they begin discriminating among different facial expressions (MacFarquhar, 2009; Leppanen & Nelson, 2009), and in early childhood, explicit face-emotion recognition emerges and rapidly progresses, with full maturation extending into early adulthood (Herba & Phillips, 2004; Thomas, De Bellis, Graham, & LaBar, 2007; De Sonneville et al., 2002; Somerville et al., 2011).
Various models for recognizing emotion from facial expressions have been proposed to account for the functional (Bruce & Young, 1986) and neuroanatomical (Haxby, Hoffman, & Gobbini, 2002; Vuilleumier & Pourtois, 2007) bases of face-emotion recognition, and have largely converged on a sophisticated model whereby visual perceptual processing decodes the structure of the face and is integrated with cognitive processing that assigns emotional and conceptual meaning (Adolphs, 2002). This is supported by evidence that mature face-emotion recognition relies on a distributed network of cortical and subcortical brain areas, including visual (fusiform gyrus, inferior and middle occipital gyri, lingual gyrus), limbic (amygdala, parahippocampal gyrus, cingulate), temporal (superior temporal gyrus), tempoparietal, and prefrontal regions, striatum, and cerebellum (Adolphs, 2002; Haxby et al., 2002; Vuilleumier & Pourtois, 2007; Fusar-Poli et al., 2009). Additionally, the recognition of specific emotions may require neural subsystems specific for that emotion that overlap and supplement general face-emotion processing circuitry (Fusar-Poli et al., 2009). Of note, the amygdala may be particularly sensitive and specific to fear processing and the insula for processing disgust (Murphy, Nimmo-Smith, & Lawrence, 2003; Fusar-Poli et al., 2009). During development, the core regions of this network are refined and strengthened, and underlie the generalized gains in face-emotion recognition (Leppanen & Nelson, 2009). Moreover, recognition for different expressions, such as anger and fear, follow varied developmental trajectories (Camras & Allison, 1985; Durand, Gallay, Seigneuric, Robichon, & Baudouin, 2007; Herba, Landau, Russell, Ecker, & Phillips, 2006) that may reflect further tuning of emotion-specific neural subsystems (Leppanen & Nelson, 2009).
The development of face-emotion recognition is not just an end unto itself; it has important downstream developmental consequences: The ability to recognize the emotions of others is necessary for important social competencies such as empathy, which promotes prosocial and cooperative behavior (Roberts & Strayer, 1996; Eisenberg & Miller, 1987). On the most basic level, empathy is sharing the experiences and emotions of others (Eisenberg & Strayer, 1987) and includes two important forms—cognitive and affective (Shamay-Tsoory, 2011). Cognitive empathy, which involves theory of mind, is a sophisticated form of cognition that requires one to take the point of view of another in order to understand his or her beliefs, intentions, and desires (Baron-Cohen, 1997; Shamay-Tsoory, 2011). Affective or emotional empathy is the ability to sense and share another’s emotional state; it involves emotion recognition and contagion (Shamay-Tsoory, 2011), and may lead to compassion, sympathetic concern, (De Waal, 2008; Nichols, 2001), and the motivation to help others (Eisenberg, 2007). Cognitive empathy and affective empathy are essentially two sides of the same empathy coin, the relative balance of the two contributing to one’s overall empathic ability (Cox et al., 2012).

Although the ability to accurately recognize the emotional state of another is necessary for empathy, the mechanism by which face-emotion recognition abilities enable empathic behavior is not completely understood. Yet the inherent relationship between face-emotion recognition and empathy is underscored by neuropsychiatric disorders characterized by distinct impairments in both domains (Blair, 2008; Nichols, 2001), and studying these phenomena in a clinical context may yield better understanding of both typical and atypical affective processing and empathy. Furthermore, extending this research into developmental populations may elucidate how early impairments in face-emotion processing lead to the empathic deficits associated with these
disorders in adulthood. Two seemingly disparate disorders in which face-emotion recognition and empathy are particularly relevant are autism spectrum disorders and psychopathy, both of which are addressed in this dissertation.

Autism spectrum disorders (ASD) are a class of neuropsychological disorders that include autism and Asperger’s syndrome. Individuals with ASD constitute a heterogeneous group with dysfunction in three core symptom clusters: deficits in communication, impaired social behavior, and the presence of restrictive and repetitive behaviors and interests (American Psychiatric Association, 2000). One of the three core symptom clusters—impaired social behavior—includes deficits in affect recognition. Face processing has been studied extensively in this population, with research spanning four decades using a variety of techniques from behavioral paradigms to functional magnetic resonance imaging (fMRI). Individuals with ASD, however, constitute a heterogeneous group with various degrees of severity and symptomology and the research findings are rife with inconsistencies. Chapter II addresses inconsistencies in affect processing studies using meta-analysis to characterize both generalized face-emotion recognition deficits and impairments in recognition of different emotions in ASD; the goal of this chapter is to quantitatively integrate a large body of literature and contribute a more complete understanding of the true nature of face-emotion recognition deficits in this population. ASD, however, are not just disorders of face-emotion recognition. Another pronounced deficit associated with impaired social behavior is diminished cognitive empathy, in which individuals have difficulty taking the perspective of another person and thus do not respond in socially appropriate ways (Baron-Cohen, Leslie, & Frith, 1985). Chapter V, in part, will address how atypical face-emotion recognition in individuals with ASD may relate to deficits in cognitive empathy.
Face-emotion recognition and empathy are also impaired in psychopathy, and in contrast to ASD, the nature of the face-emotion recognition deficits are more fully understood and deficits in empathy are related to affective—not cognitive—empathy (Blair, 2005a). Psychopathy is a disorder characterized by two factors: One factor comprised of emotional deficits including shallow affect, difficulty forming close social bonds, and reduced sympathetic concern, and a second factor encompassing impulsive antisociality (Hare, 1991; Skeem, Polaschek, Patrick, & Lilienfeld, 2011). One of the most consistent and robust features of psychopathy is a profound and selective deficit in recognizing fearful expressions while recognition of other emotional expressions remains intact (Marsh & Blair, 2008; Dawel, O’Kearney, McKone, & Palermo, 2012), akin to the “fear blindness” characteristic of patients with amygdala lesions. Structural and functional neuroimaging studies of psychopaths have provided strong evidence that amygdala dysfunction underlies these fear recognition deficits (Ermer, Cope, Nyalakanti, Calhoun, & Kiehl, 2011; Kiehl et al., 2001; Anderson & Kiehl, 2012; Blair, 2005b; Blair, 2010; Marsh et al., 2008; Jones, Laurens, Herba, Barker, & Viding, 2009; White et al., 2012), and has enhanced our understanding of the role of the amygdala in face-emotion processing.

Although the term “psychopath” is reserved for adults, psychopathy is also a developmental disorder; psychopathic adults, almost without exception, had similar traits in childhood and adolescence (Blair, Finger, & Marsh, 2009). The developmental antecedents to adult psychopathy include pediatric conduct problems and callous-unemotional traits, which are analogous to the core personality components of psychopathy, and include lack of guilt and empathy and the callous use of others (Frick & White, 2008). Amygdala dysfunction has also been implicated in youths with conduct problems and callous-unemotional traits, evidenced by
attenuated amygdala activity while viewing fearful facial expressions (Marsh et al., 2008; Jones et al., 2009; White et al., 2012) and structural abnormalities such as reduced amygdala volume relative to healthy controls (Fairchild, Stobbe, van Goozen, Calder, & Goodyer, 2010; Fairchild et al., 2011; Sterzer, Stadler, Poustka, & Kleinschmidt, 2007; Huebner et al., 2008). However, not all youths with conduct problems have high levels of callous-unemotional traits, and conduct problems in those with low levels of these traits may be associated with different neural correlates and behavioral outcomes in response to emotional facial expressions (Viding, Fontaine, & McCrory, 2012a). Research on face-emotion processing in youths with conduct problems and varying levels of callous-unemotional traits has been extremely limited, and is the subject of Chapters III and IV. Chapter III investigates the unique contributions of callous-unemotional traits and conduct problems to amygdala responses to fearful facial expressions, and Chapter IV characterizes gray matter volume differences that may underlie the behavioral phenotype in the same population of children and adolescents with conduct problems and different levels of callous-unemotional traits. How face-emotion recognition in youths with conduct problems and variations in concomitant callous-unemotional traits relates to empathic behavior, with emphasis on the results from Chapters III and IV, will also be addressed in Chapter V in concert with the discussion of face-emotion recognition and theory of mind in ASD.

The particular utility of comparing autism and psychopathy has been noted elsewhere (Blair, 2005c; Blair, 2008), and this dissertation will use the comparison as a broad framework in which to consider the development of face-emotion processing and its relation to cognitive and affective empathy. Although the full characterization of impairments in face-emotion processing
and empathy in ASD and youths with conduct problems and callous-unemotional traits is beyond the scope of this dissertation as much research is still needed, Chapters II-IV are each discrete, important contributions to this end. Chapter V integrates the findings from Chapters II-IV in the context of face-emotion recognition abilities and consequences for the development of empathy in both clinical and typically developing populations.
CHAPTER II

IMPAIRMENTS IN FACIAL AFFECT RECOGNITION ASSOCIATED WITH AUTISM SPECTRUM DISORDERS: A META-ANALYSIS

Introduction

Autism spectrum disorders (ASD) are a class of neurodevelopmental disorders that are associated with profound social impairments. These impairments include failures to form normal peer relationships, engage in reciprocal social behavior, or respond appropriately to nonverbal cues such as emotional facial expressions (American Psychiatric Association, 2000). The ability to appropriately respond to the affective facial expressions of others is thought to be essential to adaptive interpersonal functioning (Ekman, 1992), and it has been theorized that face-emotion processing deficits contribute to the social deficits that characterize ASD (Schultz et al., 2003). Empirical studies of face-emotion processing in ASD, however, have yielded contradictory results, raising questions about whether purported deficits even exist, or if they vary by age or expression (Harms, Martin, & Wallace, 2010). It has been variously suggested that individuals with autism are “as able as controls” to recognize emotional facial expressions (Castelli, 2005), that ASD affects only the recognition of fear (Pelphrey et al., 2002), or, more broadly, all “negative basic emotions” (Ashwin, Chapman, Colle, & Baron-Cohen, 2006), and that ASD affects recognition of all emotions (Rump, Giovannelli, Minshew, & Strauss, 2009). The accumulation of contradictory results hinders the generation of a consensus-based, empirically
supported, and well-accepted theory of the development of face-emotion recognition in this population, and the relationship of face-emotion processing to other social deficits in autism. Qualitative reviews have sought to integrate these research findings toward this end, but an empirical assessment of face-emotion recognition deficits in ASD is still lacking. The aim of this meta-analysis was to quantitatively determine whether ASD are associated with generalized face-emotion recognition deficits, whether deficits persist across multiple emotional expressions or are limited to specific emotions, and whether moderator variables such as age and IQ affect the magnitude of any identified deficits.

Given that diagnoses of ASD rely in part on deficient processing of nonverbal social cues, the results of experimental investigations of face-emotion recognition among individuals with ASD have yielded surprising variability. Some studies have identified generalized face-emotion recognition deficits (in which accuracy scores across all emotional facial expressions that were included in the stimulus battery are collapsed) in children (Balconi, Amenta, & Ferrari, 2012; Celani, Battacchi, & Arcidiacono, 1999; Davies, Bishop, Manstead, & Tantam, 1994; Lindner & Rosen, 2006; Rump et al., 2009; Tantam, Monaghan, Nicholson, & Stirling, 1989) and adults (Ashwin et al., 2006; Baron-Cohen, Wheelwright, & Jolliffe, 1997; Critchley et al., 2000; Humphreys, Minshew, Leonard, & Behrmann, 2007; O’Connor, 2007; Pelphrey et al., 2002; Philip et al., 2010; Wallace, Coleman, & Bailey, 2008). In others, global deficits appear driven by poor recognition performance for one or a subset of expressions, which have variously included anger, fear, disgust, sadness, and surprise (Ashwin et al., 2006; Balconi et al., 2012; Humphreys et al., 2007; Philip et al., 2010; Rump et al., 2009; Wallace et al., 2008; Wallace et al., 2011). Still others have observed specific deficits for recognition of anger (Bal et al., 2010;
Wright et al., 2008) and surprise (Baron-cohen, Spitz, & Cross, 1993; Jones et al., 2011) in the absence of global face-emotion recognition deficits. Finally, some studies have found no evidence of either global or emotion-specific impairments (Castelli, 2005; Gepner, Deruelle, & Grynfeltt, 2001; Grossman, Klin, Carter, & Volkmar, 2000; Rosset et al., 2008; Rutherford & Towns, 2008). These discrepancies suggest the influence of variables that modulate face-emotion recognition task performance and lead to inconsistent findings across studies (Harms et al., 2010), underscoring the need for quantitative characterization of face-emotion recognition deficits in ASD and the influence of potential moderator variables.

There are some indications that age may moderate the severity of face-emotion recognition deficits in ASD (Harms et al., 2010). This variable is particularly important to consider given the developmental nature of both face-emotion recognition and ASD, and previous suggestions that face-emotion recognition in ASD may progress along a distinct developmental time course, diverging from that of typically developing individuals over time (Gepner et al., 2001; Rump et al., 2009). In typically developing children, the groundwork for face-emotion recognition is evident at birth. Neonates preferentially orient their attention towards human faces over other stimuli, despite their poor visual acuity, and by five to seven months infants can reliably discriminate among emotional facial expressions (Leppanen & Nelson, 2009; MacFarquhar, 2009). Explicit face-emotion recognition begins during early childhood and develops into adulthood, with gains in both speed and accuracy (De Sonneville et al., 2002; Herba & Phillips, 2004; Thomas et al., 2007), although there are indications of a brief regression in performance during adolescence (Blakemore, 2008). Among the emerging competencies that support mature face-emotion recognition abilities are the rapid decoding and interpretation of
salient visual information, which are subserved by a distributed brain network that includes the inferior occipital gyrus, lateral fusiform gyrus, and superior temporal sulcus (STS). These areas play key roles in processing and integrating the visual aspects of faces and work in concert with emotion-processing areas such as the amygdala and orbital frontal cortex (OFC) (Leppanen & Nelson, 2009). Anatomically, this network and its basic connections are present at birth, and underlie early orienting and discrimination. Throughout development, experience refines and strengthens network connections via synaptic pruning and myelination, resulting in a mature network in late adolescence and adulthood (Leppanen & Nelson, 2009).

The developmental trajectory for face-emotion recognition varies across emotions, however. The recognition of happiness and sadness develops earliest and approaches adult-level performance by five or six years, whereas mature recognition of fear and disgust may not develop until much later (Camras & Allison, 1985; Durand et al., 2007). As a result, the gradient of age-related improvements in face-emotion recognition during development are greater for expressions like fear and disgust that undergo more protracted developmental time courses (Herba et al., 2006). This pattern of variation across emotions suggests that although some aspects of face-emotion recognition result from the progressive tuning of a core face-processing network, emotion-specific differences may reflect partially dissociable neurocognitive processes with variable structural and functional development. This variability reinforces the importance of determining whether ASD affects only the recognition of particular emotions, as impairments in recognition of, for example, fear or disgust implicates dysfunction in different neurocognitive systems than would general emotion recognition deficits (Adolphs, Tranel, Damasio, & Damasio, 1994; Marsh & Blair, 2008; Vytal & Hamann, 2010).
A second moderator variable that may be important to consider is cognitive intelligence (IQ). Although IQ is not correlated with face-emotion recognition in typically developing individuals of normal intelligence (McAlpine, Kendall, & Singh, 1991), IQ in ASD is strongly associated with performance in social cognition tasks, including face-emotion recognition (Dyck, Piek, Hay, Smith, & Hallmayer, 2006; Wright et al., 2008). It has been suggested that intelligence constitutes a compensatory mechanism in ASD (Rutherford & Troje, 2012), one that may boost performance in face-emotion recognition tasks in high IQ individuals. If individuals with ASD proceed along a different developmental trajectory than typical individuals, a compensatory mechanism would become more important later in development when abilities between those with and without ASD are most divergent. This suggests the interaction between age and IQ must also be considered.

The ability to recognize and respond to the affective states of others is critical for appropriate social reciprocity. Impairments in social interaction and responding to non-verbal cues such as emotional facial expressions are included in the diagnostic criteria for autism, and deficits in this ability are frequently described as critical to social deficits in ASD. However, the available empirical evidence provides inconsistent support for this deficit. We therefore conducted a meta-analysis to identify the nature of face-emotion processing deficits in ASD, aggregating the results of 43 studies to answer three primary questions: (1) Do individuals with ASD exhibit a generalized face-emotion recognition deficit? (2) Do deficits arise across multiple emotions, or are impairments specific to one or more basic emotions? (3) Are face-emotion recognition performance differences modulated by age, IQ, or the interaction of these variables?
Methods

Literature Search

We conducted literature searches using PubMed, Web of Knowledge, and Google Scholar to find relevant articles. Search terms included face affect, face emotion, autism, and ASD. References from articles identified using these searches were also reviewed for potentially relevant studies. Studies that met our pre-specified criteria were included in the meta-analysis.

These criteria included:

1. Studies must have included a group with one or more ASD diagnoses, including autism, Asperger’s disorder, and pervasive developmental disorder-NOS. Diagnoses were either confirmed by a clinician prior to participation in the study using objective criteria acceptable at the time of publication, such as the DSM-IV-TR (American Psychiatric Association, 2000) or ICD-10 (World Health Organization, 1993), or using a standardized diagnostic tool such as the Autism Diagnostic Interview—Revised (ADI-R) (Lord, Rutter, & Couteur, 1994), Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1989; Lord et al., 2000), or Childhood Autism Rating Scale (CARS) (Schopler, Reichler, & Renner, 1986).

2. The studies must also have included a control group for comparison. In cases where more than one control group was tested, the group that was typically developing, healthy, and chronologically age matched was included in the meta-analysis.

3. Face-emotion recognition tasks with an objective measure of accuracy (mean correct, percent correct, number of errors, etc.) must have been used. In studies that included more than one face-emotion recognition task, the task with the most prototypical and well-validated stimuli was included to increase homogeneity across studies (e.g., if recognition of both photographic
faces and cartoon faces were tested, we used only data for the photographic faces). Tasks assessing affect recognition through voice, body language, or other means were not included. Response data from studies across different experimental contexts (e.g., behavioral testing only, data recording during psychophysiological or neuroimaging testing) were included as long as accuracy for the behavioral task was reported.

4. Studies that reported accuracy results combined across multiple expressions (overall affect recognition) as well as studies that reported results for any of the six basic emotions were included.

5. Both adult and pediatric studies were included. Although adolescent development continues into the early or mid-twenties from a neurodevelopmental perspective (Blakemore & Choudhury, 2006), for the purpose of this meta-analysis the legal age of 18 was used to designate studies as either adult or pediatric. This reflects a consistent distinction in the literature: 42 of the 43 studies that qualified for inclusion in this analysis included either participants who were older than 18 or those who were younger than 18. Post-hoc comparisons between early childhood and adolescent samples were also conducted by partitioning the pediatric studies into two separate groups on the basis of a median split of average participant age.

Study Characteristics

Forty-three studies met our inclusion criteria, yielding a total sample size of 1,545 participants (ASD = 791, control = 754) (Table 1). When available, total sample size, mean participant age, percentage of females, and mean verbal, performance, and full-scale IQ were recorded for both the ASD and control groups in each study. Studies were classified as pediatric
(N = 23) if study participants were younger than 18, and otherwise as adult (N = 19). Only one study (Howard et al., 2000) reported combined results from both children and adults; the 10 participants in that study ranged in age from 15.8 to 40.3 years and the mean age was not reported. This study was therefore excluded from analyses incorporating age group or average age. Additionally, one study (Ashwin et al., 2006) reported two experiments with independent samples that met our inclusion criteria and therefore were considered to be two separate studies in the meta-analysis.
Table 1

*Characteristics of the 43 Studies Included in the Meta-Analysis*

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean (SD)</th>
<th>Min</th>
<th>Max</th>
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<tr>
<td>Study Sample Size</td>
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<td>94.58 (32.12)</td>
<td>9.10</td>
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<tr>
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<td>18</td>
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<tr>
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<td>4.60</td>
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</tr>
<tr>
<td>% Female</td>
<td>19</td>
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<tr>
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</tr>
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<td>Performance IQ</td>
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<tr>
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<tr>
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<td>109.48 (6.70)</td>
<td>96.45</td>
<td>118.69</td>
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</table>
Detailed indices of ASD diagnosis and symptom severity were infrequently and inconsistently reported. For example, in a given study the ASD participants may have received a variety of diagnoses (e.g., low functioning autism, Asperger’s disorder), but no details about number of participants, symptom severity, or behavioral results were reported for each diagnostic category. For this reason, variables that assess ASD subtype or symptom severity could not be included.

Statistical Analyses

Our first aim was to determine if there is an overall face-emotion recognition deficit in ASD. To provide us with consistent units of analysis across studies, we calculated two separate statistical variables for each study for which the required data were provided: group differences in percent accuracy (PA) and a measure of effect size (Zr), both weighted for sample size. Either or both variables were calculated for overall affect recognition (across all expressions included in the study) and specific emotions whenever possible (Table 2).
Table 2

*Studies Included in the Meta-Analysis and the Variables That Could be Calculated for Overall Face-Emotion Recognition and Individuals Emotions for Each Study*

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Mean Age (SD)</th>
<th>ALL</th>
<th>ANG</th>
<th>DIS</th>
<th>FEA</th>
<th>HAP</th>
<th>SAD</th>
<th>SUR</th>
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<td>12.00 (1.95)</td>
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<td>x</td>
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</tr>
<tr>
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<td>x</td>
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<tr>
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<td>x</td>
<td></td>
<td></td>
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<td>Bal et al., 2010</td>
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<td>10.88 (2.68)</td>
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<td>x</td>
<td>x</td>
<td></td>
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<td>x</td>
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<tr>
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<td>30</td>
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<td>x</td>
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<tr>
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<td>ALL Zr</td>
<td>ANG PA</td>
<td>ANG Zr</td>
<td>DIS PA</td>
<td>DIS Zr</td>
<td>FEA PA</td>
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<tr>
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<td>32.41 (12.35)</td>
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<td>ALL Zr</td>
<td>ANG PA</td>
<td>ANG Zr</td>
<td>DIS PA</td>
<td>DIS Zr</td>
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<td>HAP</td>
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<td>ALL</td>
<td>ANG</td>
<td>DIS</td>
<td>FEA</td>
<td>HAP</td>
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<td>SUR</td>
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<td>Tantam, Monaghan, Nicholson, &amp; Stirling, 1989</td>
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<td>Tracy, Robins, Schriber, &amp; Solomon, 2011</td>
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<td>12.25 (14.30)</td>
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<td>Wallace et al., 2011</td>
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<td>x</td>
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<td>x</td>
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<tr>
<td>Wallace, Coleman, &amp; Bailey, 2008</td>
<td>52</td>
<td>31.50 (9.00)</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Wang, Dapretto, Hariri, Sigman, &amp; Bookheimer, 2004</td>
<td>24</td>
<td>12.00 (3.65)</td>
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<tr>
<td>Wicker et al., 2008</td>
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<td>25.06 (10.46)</td>
<td>x</td>
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<td>Wright et al., 2008</td>
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<td>11.44 (2.06)</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
PA was calculated for studies that reported percent accuracy scores or data that could be converted to percent accuracy scores. In order to compare studies that used a multiple-choice format with different numbers of response options, accuracy scores were corrected for chance guessing using the formula \((\text{proportion correct} - (1/\text{number of choices}))/((1 - (1/\text{number of choices})))\) (Elfenbein & Ambady, 2002). For each study, a score expressing the difference in performance between control and ASD groups using the corrected percentage accuracy was calculated.

Difference scores were then weighted by the total sample size of the study. \(Z_r\) was calculated as a measure of effect size \((r)\) between the ASD and control groups in each study, derived from reports of Pearson’s \(r\) values or data that could be converted to \(r\) such as \(F\)-values. To account for the logarithmic scale of \(r\) values, they were normalized using a Fisher’s \(Z\) transformation then weighted by the total sample size of the study.

Both variables were included because each offers distinct advantages for the current data. PA is a metric that expresses the difference in accuracy of ASD and control groups, so it provides an intuitive measure of performance differences. Unlike \(Z_r\), a measure of variance is not required for the calculation of PA and therefore studies that failed to report standard deviation (or data from which a measure of variance could be derived) could be included using this metric. \(Z_r\) was also included because \(r\) is one of the most common and recommended measures of effect size and is often considered the gold standard for meta-analyses (Rosenthal & DiMatteo, 2001). It is a more comprehensive and (potentially more accurate) measure than PA because sample variance is incorporated in the calculation.
Data were analyzed using JMP 10 software (SAS Institute Inc., Cary NC). All statistical tests were conducted in tandem on both PA and Zr variables. Many of the studies reported data that could be transformed into both PA and Zr (Table 2), so this approach enabled us to corroborate our results across two variables and increase confidence in the reliability of our findings.

Results

Overall Facial Affect Recognition Deficits in ASD

We first assessed overall face-emotion recognition deficits in ASD across emotional facial expressions using one-sample t-tests conducted on mean PA and Zr variables. PA calculations included the results of 38 of the 43 available studies ($M_{PA} = 11.91$, $SD = 61.01$) and Zr included 34 ($M_{Zr} = .36$, $SD = 1.53$) (Table 3). For both variables, positive values indicate greater accuracy for the control group compared to the ASD group (and therefore a relative face-emotion recognition deficit in ASD). Calculations using both variables indicated that ASD is associated with significant impairments in face-emotion recognition, $t(37)_{PA} = 7.30$, $p < .001$; $t(33)_{Zr} = 7.77$, $p < .001$, with the magnitude of the effect nearly identical across the two dependent variables (Table 3). One study (Celani et al., 1999) in which accuracy between ASD and control groups differed by almost 40% was identified as a possible outlier with Mahalanobis distances of 3.33 and 2.81 for PA and Zr respectively. One-sample t-tests calculated after excluding the outlier yielded results very similar to those that included the outlier (Table 3).
Table 3

Differences in Face-Emotion Recognition Across Emotions and for Each of the Six Basic Emotions

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>ANG</th>
<th>DIS</th>
<th>FEA</th>
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|       |     |     |     |     |     |     |     |
| PA    |     |     |     |     |     |     |     |
| ASD   | 66.16 | 64.22 | 53.82 | 53.78 | 95.13 | 71.75 | 76.07 |
|       | (84.89) | (94.83) | (112.71) | (81.86) | (42.32) | (82.20) | (91.91) |
| CON   | 78.06 | 77.86 | 62.26 | 63.87 | 97.56 | 74.47 | 85.25 |
|       | (77.47) | (91.44) | (151.33) | (137.98) | (22.72) | (92.61) | (46.53) |
| M diff| 11.91 | 13.65 | 8.45 | 10.10 | 2.43 | 2.72 | 9.18 |
| (SD)  | (61.01) | (72.67) | (79.19) | (85.69) | (31.56) | (79.33) | (66.29) |
| n     | 1397 | 691 | 587 | 669 | 699 | 665 | 629 |
| t     | 7.30 | 4.94 | 2.58 | 3.05 | 2.03 | .89 | 3.47 |
| p     | < .001** | < .001** | .014* | .005** | .031* | .200 | .003** |

| Zr    |     |     |     |     |     |     |     |
| M (SD)| .36 (1.53) | .33 (1.22) | .19 (1.71) | .31 (1.54) | .15 (1.07) | .19 (1.81) | .18 (.99) |
| n     | 1109 | 634 | 491 | 612 | 644 | 636 | 533 |
| t     | 7.77 | 6.89 | 2.52 | 5.06 | 3.50 | 2.58 | 4.13 |
| p     | < .001** | < .001** | .014* | < .001** | .002** | .010* | .001** |

Note. PA = weighted, corrected percent correct difference; Zr = weighted, normalized r. N = number of studies that reported data for each emotion in total (Total), for which PA and Zr could be calculated, and number of studies for which both PA and Zr could be calculated; ALL = overall/multiple expressions; ANG = Anger; DIS = Disgust; FEA = Fear; HAP = Happiness; SAD = Sadness; SUR = Surprise.

*p < .05 ** p < .05 Bonferroni-adjusted for multiple comparisons.
Emotion-Specific Facial Affect Recognition Deficits in ASD

We next wished to determine if ASD is associated with specific deficits in the recognition of one or more emotions. Twenty-three of the 43 studies reported separate results for one or more of the six basic emotions (anger, disgust, fear, happiness, sadness, and surprise). PA and Zr variables could be calculated for 17 and 19 studies respectively (Figure 1). The number of studies that reported data on each individual emotion varied; 13 studies reported results for all 6 emotions for which results ($N_{PA} = 10; N_{Zr} = 11$) could be calculated. Due to the reduced power this limited number of studies would yield, we did not conduct $6 \times 1$ ANOVAs to identify ASD deficits in facial affect recognition across the emotions. Instead, we performed one-sample $t$-tests, applying a Bonferroni-adjusted $p$-value of .008 to correct for multiple comparisons, to identify the extent to which ASD impairs the recognition of the 6 basic emotions. The outlier study (Celani et al., 1999) identified in our initial analysis did not report results that could be transformed into PA or Zr variables for any individual emotion, so its influence was not a concern in any emotion-specific analyses.
**Figure 1.** Mean and standard error for percent accuracy difference (PA) and effect size (Zr) for overall face-emotion recognition and recognition for each of the six basic emotions.
The results of these t-tests revealed consistent, marked recognition deficits in ASD for expressions of anger, fear, and surprise. For all three emotions, tests using both PA and Zr variables showed impaired recognition of these emotions in ASD relative to controls. For happiness, ASD was associated with less accurate recognition of the expression for Zr ($p_{Zr} = .002$), but the magnitude of the effect was smaller and (not statistically significant following Bonferroni correction) for PA ($p_{PA} = .031$). For expressions of disgust and sadness, the evidence for impaired recognition in ASD was less strong (sadness: $p_{Zr} = .010$, $p_{PA} = .200$; disgust: $p_{Zr} = .014$, $p_{PA} = .014$) and did not indicate significant deficits in ASD following Bonferroni correction (because Bonferroni corrections are statistically conservative, these results should be interpreted cautiously). In summary, the results indicate face-emotion recognition deficits in ASD are not limited to one particular emotion, although they vary in severity across the 6 basic emotions (Table 3).

*Moderation of ASD Deficits by Participant Age*

We next explored how moderating variables may influence both overall and emotion-specific face-emotion recognition. To determine how age affects face-emotion recognition deficits in ASD, we first conducted separate one-sample t-tests on PA and Zr variables for emotion recognition across categories to test for the presence of deficits in both age groups. Of the 38 studies for which PA could be calculated, 23 pediatric and 15 adult studies were included in the analysis (with 18 years old the designated cutoff between groups). For the 34 studies for which Zr could be calculated, 18 pediatric and 15 adult studies were included in the analysis (Table 1). For each study, the mean participant age was calculated as a weighted average of the
chronological ages of the ASD and control participants in that particular study. As a result, each study was associated with a single value that corresponded to the mean age of all participants. The results indicated significant face-emotion recognition deficits in ASD in both the pediatric and adult samples for PA and Zr (all $p_s < .025$, Bonferroni adjusted). The results were unchanged when the previously identified outlier study (Celani et al., 1999), a pediatric study, was omitted from the analysis.

We then conducted independent samples $t$-tests comparing deficits in ASD in the pediatric studies to the adult studies to test if the magnitude of deficits differed between the two groups. The results of these tests showed some support for age as a moderator of ASD deficits in face-emotion recognition. We found marginally significant differences between deficits in children and adults for differences in accuracy, $t(36)_{PA} = 1.75, p = .089$, and significant differences for effect size, $t(31)_{Zr} = 1.33, p = .027$. Omitting the previously identified outlier study (Celani et al., 1999), both calculations ($t(35)_{PA} = 2.17, p = .037; t(30)_{Zr} = 2.91, p = .007$) showed age to be a significant moderator of ASD deficits in face-emotion recognition. Across tests, the magnitude of the performance difference between groups was greater for adult ($M_{PA} = 15.85, SD = 44.52; M_{Zr} = .47, SD = 1.46$) than pediatric ($M_{PA} = 9.28, SD = 59.38; M_{Zr} = .24, SD = 1.16$) samples, indicating more severe face-emotion deficits in adulthood. Due to the high leverage affects of the outlier study, it was removed from further analyses.

Because face-emotion recognition abilities change most profoundly during childhood (Herba & Phillips, 2004), we conducted post hoc studies comparing pediatric samples assessing ASD in early childhood and in adolescence. We conducted a median split on average participant age to divide samples into early childhood and adolescent samples ($median = 11.5$ years). This
median age approximately divides the samples into pre-pubertal and post-pubertal samples (Rogol, Roemmich, & Clark, 2002). Separate 3 (early childhood, adolescent, adult) x 1 ANOVAs for PA and Zr variables were conducted to compare face-emotion deficits in ASD across age groups. For PA, this analysis included 11 early childhood, 11 adolescent, and 15 adult studies. Results revealed a marginally significant effect of age, $F(2, 34)_{PA} = 3.16, p = .055$. Post hoc $t$-tests indicated that this effect was roughly linear in nature, with significantly greater deficits emerging in adults ($M_{PA} = 15.85, SD = 44.52$) than in early childhood samples ($M_{PA} = 6.82, SD = 46.56$), $t(34)_{PA} = 2.51, p = .017$, with the mean of adolescent samples ($M_{PA} = 11.23, SD = 67.06$) falling between the two but not significantly different from either early childhood or adult studies. A similar pattern of results was obtained using Zr scores (the analysis of which included 10 early childhood, 7 adolescent, and 15 adult studies). The results showed a significant effect of age, $F(2, 29)_{Zr} = 5.07, p = .013$ and post hoc $t$-tests indicated greater face-emotion recognition deficits in adult ($M_{Zr} = .47, SD = 1.46$) samples than in early childhood ($M_{Zr} = .19, SD = 1.35$) samples, $t(29)_{Zr} = 3.18, p = .004$, with the mean of adolescent studies ($M_{Zr} = .33, SD = .65$) falling between the early childhood and adult studies but not significantly differing from either (Figure 2). (Reduced power prevented us from conducting similar tests assessing the effects of age on specific emotions.)
Figure 2. Mean and standard error for percent accuracy difference (PA) and effect size (Zr) for overall face-emotion recognition for studies with young children, adolescents, and adults.
Because the results of our analyses supported developmental changes in the magnitude of face-emotion recognition deficits in ASD with age, we next conducted regression analyses to more sensitively assess age as a moderating variable. We conducted separate linear regressions using both PA and Zr variables with average participant age as a predictor of face-recognition deficits. Of the 41 studies included in the age-based analyses, 32 matched the average chronological age of ASD and control samples, but for 6 pediatric studies (Baron-cohen et al., 1993; Braverman et al., 1989; Buitelaar et al., 1999; Castelli, 2005; Gepner et al., 2001; Ozonoff et al., 1990) and 2 adult studies (Clark et al., 2008; Critchley et al., 2000) significant age differences existed between the ASD and control groups. In all 8 cases ASD participants were chronologically older than their control counterparts. One study (Pelphrey et al., 2002) did not provide a standard deviation for age data so a t-test could not be conducted; the mean ages were 25.20 and 28.20 years for the ASD and control groups respectively. For overall affect recognition, we found that age was a significant predictor of both PA and Zr variables, indicating that the magnitude of face-emotion recognition deficits in ASD increases with age (Table 4).
Table 4

Simple Linear Regressions on Overall Face-Emotion Recognition and Each of the Six Basic Emotions With Mean Participant Age as the Predictor

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<tr>
<th></th>
<th>ALL</th>
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<td>M diff (SD)</td>
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<td>669</td>
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<td>.008*</td>
<td>.084</td>
<td>&lt; .001*</td>
<td>.965</td>
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Note. *p < .05
Given that the developmental time course of typical face-emotion recognition is not uniform across emotional expressions (Durand et al., 2007), we conducted additional linear regressions on PA and Zr variables to assess age as a moderator variable for each emotion. To maximize power, regressions were fit separately and varying degrees of freedom reflect the inclusion of different numbers of studies (Table 4). Results showed that age was a significant predictor of deficits in the recognition of disgust, fear, and sadness for both PA and Zr variables (all ps < .01) such that the magnitude of face-emotion recognition deficits in ASD increased with age. We found weak support for increased recognition deficits for happy expressions with age ($p_{Zr} = .084; p_{PA} = .106$). Age was not found to be a significant moderator of deficits in recognizing anger or surprise ($p > .10$).

*Moderation of ASD Deficits by Participant Age and IQ*

IQ was selected as a potential moderator variable due to its association with social cognition in ASD (Dyck et al., 2006; Wright et al., 2008), sample IQ disparities between pediatric and adult studies, and the possibility of IQ-related compensatory mechanisms in ASD (Rutherford & Troje, 2012). Multiple linear regression was used to assess the influence of both age and IQ on face-emotion recognition deficits in ASD. First, separate, independent regressions were run with PA and Zr as outcome variables with average participant age, average full-scale IQ (FSIQ), and an age x FSIQ interaction term as predictors in the model. The outlier study was omitted from these analyses. For PA, 17 studies were included. The overall model was marginally significant ($R^2_{PA} = .44, F(3, 13) = 3.34, p = .053$) with age as a significant predictor in the model ($p_{PA} = .032$) while neither FSIQ ($p_{PA} = .966$) nor age x FSIQ ($p_{PA} = .136$) were
significant. Similar results were obtained for Zr, whereby the model was significant ($N_{Zr} = 11$; $R_{Zr}^2 = .83$, $F(3, 7) = 11.48$, $p = .043$) and age was a significant predictor ($p_{Zr} = .001$) but not FSIQ ($p_{Zr} = .970$). The age x FSIQ interaction term was marginally significant ($p_{Zr} = .056$) indicating the magnitude of age-related facial affect processing deficits in ASD tended to be greater in participants with lower IQs.

Analogous multiple linear regressions were also run using age and verbal IQ (VIQ) scores since many of the included studies required the use of affective labels during the task and there is evidence that language ability is related to performance ability in ASD (Wallace et al., 2008). Fifteen studies were included in the regression with PA as an outcome variable resulting in a non-significant model ($R_{PA}^2 = .21$, $F(3, 11) = .9754$, $p = .439$) and no significant terms or interactions. For Zr, 10 studies were included and the model was significant ($R_{Zr}^2 = .712$, $F(3, 6) = 4.94$, $p = .046$) with age as a significant predictor in the model ($p_{Zr} = .010$) while neither VIQ ($p_{Zr} = .142$) nor age x VIQ ($p_{Zr} = .092$) were significant. (Regressions were not run for specific emotions due to limited power: Studies that reported emotion-specific data from which PA or Zr could be calculated and included FSIQ or VIQ measures ranged in number from 6 to 11 depending on the measure of effect size, emotion, and IQ metric.)

**Discussion**

The results of this meta-analysis provided strong evidence that individuals with ASD are significantly impaired in recognizing multiple emotional facial expressions and that these deficits increase in magnitude over the course of development. This effect is robust, reflecting the results of forty-three studies consisting of 1,545 (ASD = 791, control = 754) total participants, and is
consistent with clinical observations that impaired use of nonverbal cues and reciprocal social behaviors are characteristic of ASD.

These results bring some clarity to ongoing debates about whether face-emotion recognition deficits in ASD are limited to one or more particular emotions or extend across multiple emotions. Individual studies have linked ASD to recognition deficits for various exemplars or subsets of the six basic emotions, such as fear, surprise, or negative emotions (Ashwin et al., 2006; Bal et al., 2010; Balconi et al., 2012; Baron-cohen et al., 1993; Humphreys et al., 2007; Jones et al., 2011; Pelphrey et al., 2002; Philip et al., 2010; Rump et al., 2009; Wallace et al., 2011; Wallace et al., 2008; Wright et al., 2008). However, our meta-analysis did not find evidence of deficits strongly consistent with emotion-specific theories; individuals with ASD were less accurate than controls for all six basic emotions, showing significantly worse performance for anger, fear, and surprise after adjusting for multiple comparisons. This finding is particularly important because impaired recognition of specific expressions has markedly different implications than general face-emotion processing deficits. For example, previous findings that Huntington’s disease primarily impairs recognition of disgust (Calder, Keane, Manes, Antoun, & Young, 2000; Hayes, Stevenson, & Coltheart, 2007), and that psychopathy primarily impairs recognition of fear (Marsh & Blair, 2008), implicate dysfunction in the neural structures that specifically support recognition of those emotions. Along the same lines, some have suggested that putative specific impairments in the recognition of fear or surprise suggest primary dysfunction in, respectively, the amygdala (Howard et al., 2000) or in structures supporting theory of mind (Baron-cohen et al., 1993). But the present results suggest that face-emotion recognition impairments in ASD emerge across a variety of affective facial expressions,
such that neurodevelopmental differences associated with ASD are also likely to be diffusely distributed.

*Age-Related Differences in Face-Emotion Recognition Deficits*

Our findings also explain why previous research findings have yielded inconsistent effect sizes for emotion recognition deficits in ASD: the age of study participants may be a significant moderator of group differences. We investigated age as a moderator variable using two different strategies that yielded a clear and consistent relationship between participant age and the magnitude of face-emotion recognition deficits in ASD. First, we divided the studies into those that assessed pediatric (younger than 18 years) and adult participants. Significant ASD-associated deficits were present in both age groups, but a direct comparison of the two groups via independent sample *t*-tests indicated face-emotion recognition deficits in ASD were greater in adults than in children. Using the average age of participants in each study, we further divided pediatric studies into those incorporating primarily early childhood samples versus adolescents, and used ANOVAs to compare deficits in these two groups with adult studies. We again found a strong age-based effect, with face-emotion recognition deficits in ASD least pronounced in young children followed by adolescents and adults, indicating a widening gap between individuals with ASD and controls over the course of development. Second, we conducted linear regression analyses and modeled mean participant age in each study as a predictor variable. Here again, we found the magnitude of face-emotion recognition deficits in ASD increased with age and age-related deficits for recognition of individual emotions were slightly different across expressions. We found strong evidence that deficits in recognizing disgust, fear, and sadness increase with age, moderate evidence that the same was true for happiness, and little evidence for
anger or surprise. The variability of the results may reflect the different developmental time courses for the recognition of different emotions (Herba et al., 2006).

Although research on face-emotion recognition in ASD has been conducted in both children and adults, most studies are cross-sectional and incorporate participants from a narrow age range. No previous longitudinal studies met our inclusion criteria and only one study included in our meta-analysis (Rump et al., 2009) directly compared recognition abilities across age groups. Because there is no objective criterion for behavioral deficits in face-emotion recognition, performance in individuals with ASD must be assessed via comparison to controls, such that the magnitude of deficits in this population is necessarily related to where along the developmental curve face-emotion recognition abilities are being tested. Performance deficits would thereby be expected to vary depending on the age of the participants in the study. The developmental nature of the face-emotion recognition deficits in ASD may account for some inconsistencies among the results of previous studies. A qualitative review recently hypothesized that age may moderate the severity of face-emotion recognition deficits in ASD (Harms et al., 2010), but to our knowledge, no previous study has quantitatively assessed age-related face-emotion recognition deficits in ASD.

**Divergent Developmental Trajectories for Face-Emotion Recognition**

The widening developmental gap identified by our analyses is consistent with suggestions that the acquisition of face-emotion recognition skills in typical individuals and those with ASD proceeds along distinct developmental trajectories, and that individuals with ASD may never achieve the performance level of their control counterparts (Gepner et al., 2001; Rump et al., 2009). The results of this meta-analysis suggest that the development of neural
systems that support generalized face-emotion recognition are most likely to be affected in ASD. These systems have been delineated in previous research: During typical development, brain regions supporting face-emotion recognition, such as the amygdala, fusiform gyrus and STS, undergo functional and structural maturation (Leppanen & Nelson, 2009) and face-emotion recognition abilities improve throughout early childhood (Herba & Phillips, 2004). Although growth curves may vary slightly for different affective expressions, typical individuals improve in recognition speed, accuracy, and efficiency over time, typically reaching peak accuracy levels by late adolescence (Herba et al., 2006). This improvement seems to be driven by reciprocal interactions between biological maturation and experience whereby the brain network that supports face-emotion processing is tuned through exposure to facial affect—obtained through everyday interactions with others—which leads to further and more specialized experience with these nonverbal cues (Leppanen & Nelson, 2009) and contributes to age-related increases in face-emotion recognition performance.

Exactly how the developmental trajectory of face-emotion recognition in ASD diverges from that of typically developing children and adolescents is not yet well understood. However, the results of our meta-analysis are consistent with suggestions that face-emotion recognition abilities in this population remain essentially flat over time rather than steadily improving from childhood to adulthood (Gepner et al., 2001; Rump et al., 2009). A variety of aberrant processes may underlie this flat trajectory. Neural structures and connections important for face-emotion processing may differ from those of typical individuals very early in development (Courchesne, Redcay, & Kennedy, 2004; Sparks et al., 2002), with downstream consequences for facial affect recognition. For example, young children with ASD do not show a visual preference for human
faces, lack spontaneous gaze to emotionally salient facial features, and have impaired joint attention abilities (Dawson et al., 2004). Abnormal gaze patterns continue throughout development, marked by reduced eye contact (Mundy, Sigman, Ungerer, & Sherman, 1986) and atypical visual scan paths when looking at faces (Pelphrey et al., 2002). This suggests that a breakdown in the mutually reinforcing gains in biological maturation and experience characteristic of typical development may attenuate improvements in face-emotion recognition as individuals with ASD mature (Grelotti, Gauthier, & Schultz, 2002; Sasson, 2006). Reciprocal interactions between brain networks that are inherently different from those of typical individuals and limited experience with facial affect, perhaps driven in part by abnormal gaze patterns, may drive ongoing atypical development of face-emotion recognition.

Some have argued that generalized face-emotion recognition deficits in ASD reflect atypical development specifically in the fusiform gyrus, a critical region of the “social brain” and a region implicated in many aspects of human face processing (Kanwisher, McDermott, & Chun, 1997; Raine et al., 2006). One of the prevailing theories is that the fusiform gyrus activation reflects the development of visual expertise (Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999; Gauthier, Skudlarski, Gore, & Anderson, 2000), and improvements in the speed and accuracy of face-emotion processing characteristic of facial affect expertise may reflect increased functional reliance on the fusiform gyrus (Nelson, 2001). Functional expertise may also be supported by the predominant use of configural and holistic processing (Gauthier & Tarr, 1997; Mondloch, Le Grand, & Maurer, 2002), an efficient cognitive strategy that utilizes the spatial relations among facial features, rather than the appearance of individual features in isolation.
Fusiform dysfunction has been implicated in face-emotion recognition deficits in ASD in part because these neurocognitive hallmarks of face-emotion expertise are absent in individuals with this disorder. Those with ASD often fail to develop configural or holistic processing strategies (Joseph & Tanaka, 2003), instead relying on inefficient featural processing throughout development (Happé & Frith, 2006). The results of neuroimaging studies suggest that, in ASD, activation in the lateral fusiform gyrus may be attenuated during face-emotion recognition tasks (Critchley et al., 2000; Schultz et al., 2000) and reflect deficits in a core social cognitive mechanism (Schultz et al., 2003). However, when individuals with ASD are explicitly directed to orient their gaze to faces, fusiform gyrus activation approaches that of typical individuals (Dalton et al., 2005), indicating that function in this region is preserved to the extent it can respond to human faces at least in some contexts. In addition, studies featuring social stimuli with which individuals with ASD have extensive expertise, such as familiar cartoon characters, have found typical patterns of fusiform recruitment (Grelotti et al., 2005) and configurally-based processing (Rosset et al., 2008). These findings suggest that rather than profound deficits in functioning in the fusiform gyrus being critical to face-emotion recognition deficits in ASD, atypical patterns of fusiform activation in previous neuroimaging studies may reflect strategic differences in face processing in individuals with this disorder.

The importance of strategy for efficient face processing was also supported by the results of our analyses examining the moderating effects of intelligence. Cognitive intelligence has been shown to affect performance in a variety of social cognition tasks in individuals with ASD, suggesting that it may provide a compensatory mechanism that confers a face-emotion recognition advantage (Rutherford & Troje, 2012; Dyck et al., 2006). Our data provided some
evidence in favor of the possibility of such compensatory processes. Higher full-scale IQ scores were found to mitigate age-related deficits in ASD, with the greatest IQ-conferred advantages observed in adulthood, a time when face-emotion recognition deficits are generally most pronounced. This suggests that high-IQ individuals with ASD may develop effortful cognitive strategies for understanding the fleeting and complex changes to the appearance of the face that accompany emotion, which they can employ at least in the context of laboratory tasks. It is unclear from our findings whether these strategies can also be effectively deployed in naturalistic settings. If evidence supports the possibility that deliberate strategies can be used to reduce face-emotion processing deficits in adults with ASD, however, then it would favorably support the goal of training children and adolescents with ASD to read faces using robots or computer training tasks, although evidence for the efficacy of such programs as they are currently implemented is mixed (Ramdoss et al., 2012). The need for effective interventions is clear given that face-emotion recognition deficits in ASD appear not to naturally normalize over time, but rather increase in severity, and that a lack of expertise in social skills like face-emotion recognition may contribute to profound deficits in communication and social functioning in adults with ASD (Boraston et al., 2007; Humphreys et al., 2007).

Considerations and Limitations

Our results should be interpreted in the context of some limitations inherent in the meta-analytic process as well as those that reflect omissions typical of studies of ASD. For example, a number of studies of face-emotion recognition did not provide sufficient information to permit their inclusion in emotion-specific analyses and regressions with IQ, reducing power for these analyses. Some studies only tested responses to a few of the six expressions typically included in
face-emotion recognition studies, which also limited our ability to compare the magnitude of observed effects across all expressions. Finally, not all studies reported values that could be converted to a common metric. The effects of some differences in reported statistics could be mitigated by our use of two different measures of effect size. And the strong correspondence in the results between the two variables, despite incorporating slightly different studies with different expressions, increases our confidence in our results.

Perhaps a more important consideration is that, in general, no data were available to permit analysis of how variability of ASD subtypes (e.g., autism, Asperger’s disorder, pervasive developmental disorder—not otherwise specified) and symptom severity affect face-emotion recognition ability. It is very likely these differences account for real recognition differences, and may also contribute to discrepant findings in the literature (Balconi et al., 2012; Harms et al., 2010). Moreover, because many studies assess face-emotion recognition using paradigms that require basic verbal competency or are physically taxing (e.g., neuroimaging, eye-tracking, or psychophysiological studies that require long periods of concentration or stillness and tolerance of unfamiliar machinery touching the face), it is primarily the results of studies employing very high-functioning individuals that are included in literature. But because little concrete evidence is available to determine whether diagnosis or level of functioning influences face-emotion recognition abilities, we cannot know how these sampling biases influence the patterns of results we have observed.

Conclusions

Our meta-analysis integrated a large and variable body of research results that has not been previously assessed quantitatively. Our results offer an empirical framework within which
to understand face-emotion recognition deficits in ASD and interpret both past and future research findings. Moreover, it supports a developmental theory of face-emotion recognition deficits in this population: Our results indicate that individuals with ASD exhibit a strong, generalized deficit in face-emotion recognition, and that the magnitude of this deficit increases during development. This relative deficit may be driven by improvements in typically developing children and adolescents that reflects both the maturation of neuronal circuits that underlie the recognition of facial affect and experience-dependent expertise for recognizing emotional expressions. Face-emotion recognition in individuals with ASD may proceed along a distinct developmental trajectory that impedes the acquisition of mature face-emotion recognition abilities. This deficit, most pronounced in adulthood, may contribute to broader social impairments in ASD that are characterized by inappropriate use of nonverbal cues.
CHAPTER III

AMYGDALA RESPONSE TO FEAR MEDIATES THE RELATIONSHIP BETWEEN CALLOUS-UNEMOTIONAL TRAITS AND PROACTIVE AGGRESSION AMONG CHILDREN WITH CONDUCT PROBLEMS

Introduction

Externalizing behaviors and conduct problems are among the primary reason youths in the United States are referred to psychiatric care (Kessler et al., 2005). However, there remains a dearth of effective risk assessment and treatment strategies, partly due to heterogeneity among children and adolescents with antisocial behavior (Frick, 2012).

Youths with conduct problems can be distinguished by the presence or absence of callous-unemotional traits, which include reduced empathy and remorse and shallow affect (Frick & Moffitt, 2010), and which are associated with more severe, persistent, and treatment refractory externalizing behaviors (Lynam, Loeber, & Stouthamer-Loeber, 2008). Conduct problems in youths with and without callous-unemotional traits are thought to emerge from distinct etiological trajectories (Barker et al., 2010). However, because conduct problems and callous-unemotional traits are positively correlated, statistical suppressor effects may impede understanding of the unique neurobiological correlates of these variables. This has led to an increasing emphasis on the importance of treating these variables as continuously varying traits and employing analyses that simultaneously model both to account for their covariance (Hicks & Patrick, 2006; Sebastian et al., 2012). The present study assesses whether patterns of
neurobiological functioning among youths with conduct problems who vary in callous-unemotional traits are better captured by analyses that simultaneously model both externalizing behaviors and callous-unemotional traits as continuous variables than by analyses that dichotomize these variables. It also assesses whether such analyses can demonstrate that specific patterns of neurobiological dysfunction mediate the relationship between callous-unemotional traits and the characteristic behavioral phenotype of proactive aggression that is associated with these traits.

Callous-unemotional traits in children with conduct problems are consistently linked to disrupted functioning of the amygdala, particularly reduced responses to socio-affective cues like fearful expressions (Marsh et al., 2008; Jones et al., 2009; White et al., 2012; Viding et al., 2012b). Because fearful expressions elicit empathy and inhibit aggression in adults and typically developing youths (Blair, 2005d; Marsh & Ambady, 2007), reduced responsiveness to these cues is thought to mediate the increase in proactive, or goal-directed, aggression observed in youths with callous-unemotional traits (Crowe & Blair, 2008; Blair, 2005d). However, this causal pathway has not been directly tested.

In contrast to youths with elevated callous-unemotional traits, youths with conduct problems (particularly adolescent-onset conduct problems) and low levels of callous-unemotional traits exhibit elevated activity in the amygdala, insula, and striatum in response to socio-affective stimuli (Herpertz et al., 2008; Passamonti et al., 2010). This is consistent with observations of primarily reactive aggression in these youths (Blair, 2012; Polier, Herpertz-Dahlmann, Matthias, Konrad, & Vloet, 2010; Crowe & Blair, 2008), and with hypotheses that their externalizing behaviors reflect emotional dysregulation and elevated threat sensitivity rather
than reduced empathy (Frick, 2012). Thus, although callous-unemotional traits are positively correlated with externalizing behaviors, these variables are, respectively, negatively and positively correlated with amygdala responses to socio-affective stimuli. This pattern can result in statistical suppressor effects, which occur when two correlated predictors exhibit opposite relationships with a criterion variable (Hicks & Patrick, 2006).

Despite this pattern, and despite growing consensus regarding the importance of modeling callous-unemotional traits as continuous variables (Edens, Marcus, Lilienfeld, & Poythress, 2006; Guay, Ruscio, Knight, & Hare, 2007), most neuroimaging research in youths with conduct problems and callous-unemotional traits treats these variables dichotomously (White et al., 2012; Jones et al., 2009; Marsh et al., 2008; Finger et al., 2011). We aimed to directly compare the efficacy of this approach and a regression-based approach capable of accounting for suppressor effects in a study that identified neurobiological correlates of callous-unemotional traits and externalizing behaviors using functional magnetic resonance imaging (fMRI). We scanned healthy controls and youths with conduct problems who varied in callous-unemotional traits and hypothesized that regression-based analyses would more effectively capture predicted patterns of amygdala responsiveness than would analysis of variance. We also hypothesized that regression-based analyses would find that decreased amygdala activation in response to fearful expressions mediates the relationship between callous-unemotional traits and proactive aggression, suggesting that amygdala hypoactivation serves as an intermediate phenotype.
Methods

Participants

Following study approval by the Georgetown University Institutional Review Board, youths ages 10 to 17 were recruited from the Washington, DC community via fliers, brochures, and advertisements. Written informed consent and assent were obtained from parents/guardians and participants, respectively, and children and parents completed a battery of assessments. All participants had an estimated full-scale IQ of at least 80 measured by the Kaufman Brief Intelligence Test-2 (K-BIT) (Kaufman, 1990) and reported no history of head trauma or neurological disorder. All youths were medication-free at the time of scanning, with the exception of five youths with conduct problems and one control for whom psychiatric medication could not be withheld prior to scanning; the control was excluded from all analyses. Data from four participants (1 healthy control and 3 with conduct problems) were excluded due to excessive movement during scanning. Qualified participants (n = 46) were 30 youths with conduct problems and 16 healthy controls (Table 1). For all group-based analyses, youths with conduct problems were divided into two groups post-hoc: Those with low callous-unemotional traits (n = 16) and those with high callous-unemotional traits (n = 14) following a median split on maximum scores on the Inventory of Callous-Unemotional Traits.
Table 1

Demographic and Clinical Characteristics of Participants with Conduct Problems and Healthy Controls

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>Healthy Controls (n = 16)</th>
<th>Conduct Problems (n = 30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic variables, mean (SD)</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Male : Female ratio</td>
<td>10 : 6</td>
<td>16 : 14</td>
<td>.76</td>
</tr>
<tr>
<td>Age</td>
<td>12.75 (2.41)</td>
<td>14.74 (2.46)</td>
<td>.01*</td>
</tr>
<tr>
<td>Cognitive intelligence</td>
<td>112.69 (15.38)</td>
<td>98.10 (9.73)</td>
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</tr>
<tr>
<td><strong>Behavioral measures, mean (SD)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Child Behavioral Checklist</td>
<td>43.38 (9.47)</td>
<td>72.70 (4.94)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Inventory of Callous-Unemotional Traits</td>
<td>25.50 (6.66)</td>
<td>44.28 (8.31)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Reactive Proactive Questionnaire</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Reactive aggression</td>
<td>6.12 (4.29)</td>
<td>12.47 (4.46)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Proactive aggression</td>
<td>0.88 (1.09)</td>
<td>6.40 (5.54)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>fMRI task accuracy (%)</td>
<td>92.79 (6.69)</td>
<td>93.21 (4.99)</td>
<td>.81</td>
</tr>
</tbody>
</table>

Note. Full-scale IQ from KBIT-2, Child Behavior Checklist scores are the age and gender standardized t-scores of externalizing behavior (items measuring aggression and rule-breaking), and the Inventory of Callous-Unemotional Traits scores is derived from the maximum score on each item from the parent and youth versions. Asterisk (*) denotes significant group differences at p < .05, two-tailed, measured with t-tests except for gender (Fisher’s exact test).
Assessment Instruments

Parents completed The Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997; Viding et al., 2012b) and The Child Behavior Checklist (CBCL) (Achenbach, 1991) to assess conduct problems. The SDQ is comprised of 25 questions that measure emotional symptoms, hyperactivity, peer problems, prosocial behavior, and conduct problems, and a score \( \geq 4 \) on the conduct problems scale indicates clinically significant conduct problems (Goodman, 1997). The Child Behavior Checklist (CBCL) (Achenbach, 1991) is a diagnostic tool used to differentiate clinical and typically developing samples, including those with conduct disorder (Jensen et al., 1996), and contains a subscale explicitly designed to measure externalizing behaviors such as violence and aggression. An age and gender normalized \( t \)-score \( \geq 65 \) on the externalizing behavior subscale of the CBCL signifies clinically significant externalizing behaviors (Achenbach, 1991) and was used as an estimate of conduct problems. Participants who met criteria for conduct problems on both the SDQ and CBCL were included in the conduct problems group; healthy controls did not meet criteria for conduct problems on either measure.

Participants and parents separately completed The Inventory of Callous-Unemotional Traits (ICU) (Kimonis et al., 2008), comprised of 24 items that measure callous-unemotional traits in youths. Participants and a parent separately rated each item using a 4-point scale, and for each item, the highest numeric response given by either the participant or parent was selected and summed as a measure of callous-unemotional traits (Jones et al., 2009; Sebastian et al., 2012). This scoring method is recommended, rather than a summative or averaging approach, to account for reporter bias and discrepancies (Roose, Bijttebier, Decoene, Claes, & Frick, 2010).
Aggressive behavior was assessed using the participant-completed Reactive Proactive Aggression Questionnaire (RPQ), a 23-item questionnaire that separately measures reactive and proactive aggression (Raine et al., 2006).

\textit{fMRI Task}

During scanning, participants completed an implicit face-emotion processing task used in previous studies of children with conduct problems and callous-unemotional traits (Marsh et al., 2008). Stimuli consisted of images from the Pictures of Facial Affect series (Ekman & Friesen, 1976) of ten men and women displaying positive-neutral, fearful, and angry expressions. Positive-neutral stimuli were morphs of neutral and happy expressions at twenty-five percent happiness. Fearful and angry expressions included both full-intensity natural expressions and morphed expressions of fifty percent and one hundred fifty percent intensity levels. Hair, ears, neck, and clothing were masked and faces appeared against a black background in randomized order for two seconds, followed by a one-second fixation cross. The task featured an implicit processing paradigm such that participants indicated the gender of each face rather than the expression via button press (Marsh et al., 2008; Jones et al., 2009). The task included four 5.5 minute consecutive runs, each containing 80 face trials and 20 jittered inter-stimulus interval trials.

\textit{Image Acquisition}

MR images were acquired with a 3T Siemens Tim Trio scanner (Siemens Medical Solutions, Erlangen, Germany) and 8-channel phased-array head coil. Functional data were collected using a T2*-weighted echo-planar imaging (EPI) sequence with the following parameters: TR = 3000 ms, TE = 30ms, 3.0 mm voxels, 56 slices, 64 x 64 matrix, FOV = 192
mm. A high-resolution T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) structural scan was collected for each subject (TR = 1900 ms, TE = 5.52 ms, 1.0³ mm voxels, 176 slices, 246 x 256 matrix, FOV = 250 mm).

Image Analysis

Data were processed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Prior to preprocessing, the first four volumes of each functional run were excluded, yielding 106 volumes for each of four functional runs. EPI images were slice time corrected, realigned, co-registered, normalized into MNI space, smoothed with an 8 mm Gaussian kernel, and written out to 2 mm³ isometric voxels. Realignment parameters were examined to ensure head movement did not exceed one voxel/TR, and, as noted above, four participants were excluded from analysis due to excessive motion. All preprocessed images were visually inspected for image quality. At the individual level, a design matrix was created for each participant that included regressors for each stimulus type (fear at full intensity, anger at full intensity, etc.), incorrect/non-response trials, and six motion parameters. Contrast images were generated for each stimulus type over implicit baseline for group level analyses.

At the group level, we conducted both region of interest (ROI) and whole-brain analyses. ROI analyses. Using MarsBaR (Brett, Anton, Valabregue, & Poline, 2002), we constructed a 6mm spherical right amygdala ROI centered at coordinates xyz = 24, -5, -13, obtained from a recently published study on juvenile conduct problems (Sebastian et al., 2012). We conducted both analysis of variance and multiple regression analyses constrained to this ROI to identify the roles of externalizing behaviors and callous-unemotional traits in patterns of amygdala activation in response to full-intensity fearful expressions. To assess the sensitivity of our regression
approach to previous approaches that created sub-groups of individuals with conduct problems, we conducted a one-way ANOVA on three groups (healthy controls, conduct problems/low callous-unemotional traits, and conduct problems/high callous-unemotional traits), with age and cognitive intelligence as covariates of no interest. Multiple regression analyses were also conducted that assessed amygdala activation both across the entire sample (again including age at testing and cognitive intelligence scores as covariates) and separately for only children with conduct problems. ROI analyses were thresholded at \( p < .05 \) FWE.

In addition, we conducted two whole-brain multiple regression analyses, one that included healthy controls and children with conduct problems and another that included only children with conduct problems. Both externalizing behaviors and callous-unemotional traits were simultaneously modeled as continuous variables following emerging consensus that this analytic strategy most effectively captures the latent structure of both phenomena and would allow us to identify the unique contributions of each variable (Sebastian et al., 2012; Markon, Chmielewski, & Miller, 2011). Age at testing and cognitive intelligence scores were included as covariates of no interest to account for group differences in these variables. Analyses were thresholded at \( p < .005 \) and \( k = 10 \) voxel cluster extent, a combination that has been demonstrated to produce a desirable balance between type I and II errors as is more appropriate for investigating complex cognitive and emotional effects than other correction methods (Lieberman & Cunningham, 2009; White et al., 2012).

Finally, to interrogate the role of the amygdala as a potential mediator of proactive aggression, amygdala parameter estimates averaged across the independent spherical ROI were extracted from each contrast and tested as potential mediator variables. We performed a
bootstrap mediation analysis using the INDIRECT macro implemented in SPSS 18 (Preacher & Hayes, 2008). This procedure uses nonparametric resampling to test mediation and does not require normality assumptions; this approach has been recommended over other types of mediation analysis such as the Sobel test, causal steps, and distribution of the product approaches due to high power, good control over Type I error rates, and ability to be used in small samples (Preacher & Hayes, 2004; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). Rather than providing formal p-values, this method uses bootstrap confidence intervals of the indirect effect to test significance, whereby confidence intervals that do not contain zero are indicative of mediation.

Results

Behavioral Responses

All participants performed above chance on the gender discrimination task performed inside the scanner. Total accuracy was 92.79% (SD = 6.69%) for healthy controls and 93.21% (SD = 4.99%) for youths with conduct problems and not significantly different, t_{44} = .24, p = .81. There were no group differences for individual emotions or significant correlations with age or cognitive intelligence (ps > .05). Incorrect and non-response trials were omitted from fMRI analyses.

ROI Analyses

The results of our 3-group one-way analysis of variance found no significant effect of group in the amygdala following FWE correction. The results of a second analysis of variance, including severity of externalizing behaviors as an additional covariate of no interest, again found no significant main effect of group.
By contrast, the results of a multiple regression analysis across the full sample found that responses in the right amygdala were positively associated with externalizing behaviors ($xyz = 24, 0, -14; k = 8$) and negatively associated with callous-unemotional traits ($xyz = 26, 0, -12; k = 1$) as hypothesized. A second regression restricted to only youths with conduct problems found similar but more robust results: right amygdala activity was positively associated with externalizing behavior ($xyz = 26, -4, -12; k = 47$) and negatively associated with callous-unemotional traits ($xyz = 26, 0, -12; k = 11$) (Figure 1).
Figure 1. Results of a Regression Analysis in Right Amygdala Region of Interest. Right amygdala responses to full-intensity fearful expressions were contrasted over implicit baseline. Center: Results of a multiple regression analysis including 30 participants with conduct problems found activation restricted to the 6mm spherical ROI was positively associated with externalizing behaviors (red voxels) and negatively associated with callous-unemotional traits (blue voxels), with overlapping areas in yellow, $p < .05$ FWE. Top and bottom: Leverage plots show the unique association between mean beta values extracted from the entire amygdala ROI and (a) externalizing behaviors and (b) callous-unemotional traits after accounting for the variance of the other.
We confirmed that these patterns of results were limited to responses to fearful expressions. Parallel ROI regression analyses examining responses to full intensity angry expressions and neutral expressions found no associations between right amygdala activation and either externalizing behavior or callous-unemotional traits. No significant associations were found in response to neutral expressions in the full sample, but when the sample was limited to youths with conduct problems, we found that right amygdala responses to neutral expressions were positively associated with externalizing behaviors ($xyz = 24, -8, -16; k = 17$).

**Whole-Brain Analyses**

Across the entire sample, the results of whole-brain multiple regression analyses confirmed that amygdala responses to fearful expressions were positively associated with externalizing behaviors (controlling for callous-unemotional traits) in clusters that included the right caudate nucleus ($xyz = 12, 2, 20; k = 303$), putamen and amygdala ($xyz = 26, 4, -12; k = 161$), and a cluster in right superior temporal gyrus ($xyz = 62, -6, -10; k = 876$) that extended into the orbitofrontal cortex and insula, as well as the left superior frontal gyrus ($xyz = -22, 66, 10; k = 15$). Conversely, regions negatively associated with callous-unemotional traits (controlling for externalizing behaviors) included a large cluster ($xyz = 14, -2, 18; k = 1276$) containing the right caudate, putamen, and amygdala, right inferior frontal gyrus ($xyz = 44, 26, -14; k = 42$) and several clusters bilaterally that extended into the right insula. Reported coordinates signify the location of peak voxel intensity within the cluster according to the MNI atlas (Table 2). Comparable results emerged when these results were limited to only children with conduct problems.
Table 2

*Regions of Activation Positively and Negatively Associated with Conduct Problems and Callous-Unemotional Traits*

<table>
<thead>
<tr>
<th>Anatomical Regions</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>k_v</th>
<th>Z</th>
<th>p</th>
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<td>14</td>
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<td>Anatomical Regions</td>
<td>x</td>
<td>y</td>
<td>z</td>
<td>k_e</td>
<td>Z</td>
<td>p</td>
</tr>
<tr>
<td>------------------------------------</td>
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<td>------</td>
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</tr>
<tr>
<td>Caudate</td>
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<tr>
<td>Temporal pole</td>
<td>54</td>
<td>12</td>
<td>-18</td>
<td>266</td>
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<td>&lt;.001</td>
</tr>
<tr>
<td>Precentral gyrus</td>
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<td>10</td>
<td>30</td>
<td>51</td>
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<td>.002</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
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<td>-20</td>
<td>58</td>
<td>21</td>
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<td>.002</td>
</tr>
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<td>Middle temporal gyrus</td>
<td>58</td>
<td>-40</td>
<td>-10</td>
<td>158</td>
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<tr>
<td>Inferior parietal lobule</td>
<td>-28</td>
<td>-50</td>
<td>38</td>
<td>46</td>
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<td>.001</td>
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<tr>
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<td>48</td>
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<td>Inferior occipital gyrus</td>
<td>-48</td>
<td>-74</td>
<td>-14</td>
<td>253</td>
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<tr>
<td>Superior occipital gyrus</td>
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<td>-80</td>
<td>34</td>
<td>47</td>
<td>3.44</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Middle occipital gyrus</td>
<td>-24</td>
<td>-84</td>
<td>24</td>
<td>114</td>
<td>3.15</td>
<td>.001</td>
</tr>
</tbody>
</table>

*Note.* Whole-brain regression analyses in 46 participants with scores of age and cognitive intelligence as covariates of no interest. Results thresholded at $p < .005$, $k = 10$. Coordinates reported in MNI space.
Mediation Analysis

We conducted bootstrap mediation analysis restricted to youths with conduct problems, in which callous-unemotional traits, parameter estimates of amygdala activity drawn from our ROI analyses, and proactive aggression were modeled as the independent, mediating, and dependent variables respectively, with externalizing behaviors included as a covariate. Results revealed a 95% bias-corrected confidence interval for the indirect effect size that excluded zero (.01, .34), and therefore indicated a significant indirect effect of callous-unemotional traits on proactive aggression through the amygdala (Preacher & Hayes, 2004) (Figure 2). A parallel analysis found that amygdala activation did not mediate the relationship between callous-unemotional traits and reactive aggression, 95% bias corrected confidence interval of (-.08, .19).
Figure 2. Amygdala Response Mediates the Relationship Between Callous-Unemotional Traits and Proactive Aggression. 95% bias-corrected confidence interval for the indirect effect from a bootstrap mediation analysis that found right amygdala responses to fearful expressions mediated the relationship between callous-unemotional traits and proactive aggression among 30 youths with conduct problems.
Discussion

The results of this study confirmed that amygdala responses to fearful facial expressions are differentially associated with externalizing behaviors and callous-unemotional traits, and that the amygdala mediates the relationship between callous-unemotional traits and proactive aggression. This study also confirmed the presence of suppressor effects that reduce the efficacy of group-based dichotomous analyses (analysis of variance) in identifying neurobiological distinctions among youths with conduct problems who vary in callous-unemotional traits. These findings suggest that amygdala responses to fearful expressions may represent an intermediate phenotype that links callous-unemotional traits in youths with conduct problems to an important behavioral phenotype, but that identifying this effect requires holding externalizing behavior constant. This research also extends prior neuroimaging research on callous-unemotional traits in several important respects: This is the first study of both male and female youths with conduct problems and both high and low levels of callous-unemotional traits, and the first to compare responses to supraliminal fearful, angry, and neutral expressions. That the hypothesized effects were observed in response to fearful but not angry or neutral facial expressions reinforces the moderating role of responses to fearful expressions in particular in empathic and aggressive behavior (Marsh & Ambady, 2007; Blair, 2005d).

Previous studies of adolescents with conduct problems and callous-unemotional traits have linked the recognition of fearful facial expressions to aggressive behaviors and empathic responsiveness (Marsh & Blair, 2008), and shown that, relative to healthy controls, adolescents with elevated conduct problems and callous-unemotional traits exhibit amygdala hypoactivation
to these cues (Jones et al., 2009; Marsh et al., 2008; White et al., 2012). However, these studies have been limited by their inability to disentangle the neurobiological correlates of externalizing behaviors and callous-unemotional traits. More recent studies have assessed adolescents with varying levels of callous-unemotional traits and found that these traits—rather than conduct problems—predict amygdala hypoactivation (Sebastian et al., 2012; Viding et al., 2012b).

Although the importance of simultaneously modeling callous-unemotional traits and externalizing behaviors has been described (Sebastian et al., 2012), no previous study has simultaneously modeled callous-unemotional traits and externalizing behaviors in response to fearful expressions and compared the efficacy of this technique to that of group-based analysis. In addition, no prior study has linked the resulting patterns of neural activation to aggressive behavior. The present findings reinforce the importance of considering both callous-unemotional traits and externalizing behaviors simultaneously, and suggest studies of undifferentiated conduct disorder may fail to capture critical distinctions among subpopulations of affected youths.

The amygdala plays a critical role in aggressive and violent behavior. Chronic hyperactivity in the amygdala and other components of the neural fear circuit as a result of environmental and genetic factors is implicated in reactive aggression, defined as an angry or aggressive response to provocation (Blair, 2012; McCrory, De Brito, & Viding, 2010). Responses to perceived threat follow a gradient as a function of threat severity and proximity (Gray & McNaughton, 2000). Elevated threat responsiveness results in individuals who are hypersensitive to fear-relevant cues engaging in aggressive behavior in response to even mildly threatening or ambiguous stimuli. The observed positive relationship between externalizing behaviors and amygdala responses to both fearful expressions and neutral in the present study
may reflect the tendency of externalizing youths to overreact to fear-relevant socio-affective cues.

In contrast to reactive aggression, proactive aggression is an emotionally “cool” form of aggression used to achieve instrumental goals (Blair, 2005d). Proactive aggression is consistently linked to callous-unemotional traits and empathy deficits in both adolescents and adults (Blair, 2007; Blair, 2005d). It is for this reason that aberrant responses to salient victim distress cues like fearful facial expressions are thought to reliably distinguish among individuals with conduct problems with low versus high levels of callous-unemotional traits, as victim distress cues normally elicit empathy and inhibit aggression in typically developing children and adults (Dawel et al., 2012; Marsh & Blair, 2008; Sylvers, Brennan, & Lilienfeld, 2011). But reduced amygdala activation in responses to fearful expressions (a salient form of distress cue) has not previously been found to link callous-unemotional traits to proactive aggression. In addition to confirming this link, we found that amygdala hypoactivation in youths with elevated callous-unemotional traits uniquely predicts proactive aggression; no similar relationship was found with reactive aggression. This pattern is consistent with hypotheses that proactive, but not reactive, aggression results from dysfunctional empathic responses to victim distress in youths with elevated callous-unemotional traits.

Several limitations of this study should be noted. Our study employed research assessments of conduct problems and callous-unemotional traits rather than clinical assessments. Previous studies employing both clinical (Marsh et al., 2008; White et al., 2012) and research (Jones et al., 2009; Viding et al., 2012b) assessments have yielded markedly similar results, but it will be important to determine whether our findings characterize clinically assessed youths. In
some case our groups differed in age and/or cognitive intelligence; to account for this we included age and cognitive intelligence as covariates of no interest in our analyses. Also, medication in five adolescents with conduct problems could not be withheld prior to scanning, although previous examinations of this issue suggest that these medications are unlikely to critically influence the observed effects (Marsh et al., 2013; Finger et al., 2008). Finally, rather than using an anatomically defined ROI, we chose to use a spherical amygdala ROI centered on coordinates from a study in youths with conduct problems that had obtained these coordinates by averaging peak amygdala activation in similar studies with the same population (Sebastian et al., 2012). While this approach might not capture the full magnitude of activation across the region, it is a very important methodological consideration given that we found reduced amygdala volume in our sample of youths with conduct problems, the results of which are detailed in Chapter IV. Using an ROI based on anatomical boundaries defined by a typical population could potentially overestimate the size of the amygdala in a population with less volume in this area and taint results by inadvertently including activation in regions outside the amygdala. Here, a more targeted spherical ROI is less likely to be affected by inconsistencies in functional/structural boundaries between populations.

Despite these limitations, our study extends previous findings regarding youths with conduct problems. We showed that consciously processed fearful expressions result in distinct patterns of amygdala activation that correspond to varying levels of callous-unemotional traits and externalizing problems in a mixed-gender sample and are also related to characteristic patterns of aggressive behavior. The present findings support the utility of a callous-unemotional traits specifier for the assessment of children with conduct problems and highlight the increased
sensitivity and power that results from treating clinical measures as dimensional rather than dichotomous variables (Frick & Moffitt, 2010). Our findings also provide the first evidence that identified patterns of neural responses in adolescents with conduct problems who vary in callous-unemotional traits apply to both male and female adolescents.

Heterogeneity among youths with conduct problems has historically represented an impediment to the development of improved risk assessment, diagnosis, and treatment strategies (Frick, 2012). The present findings link observable patterns of aggressive behavior with specific patterns of neural dysfunction in youths with conduct problems who present with varying levels of callous-unemotional traits. These findings confirm the importance of considering temperamental and personality variables in addition to behavior patterns in formulating effective, targeted treatment approaches for youths with conduct problems.
CHAPTER IV
GRAY MATTER VOLUME DIFFERENCES IN CHILDREN AND ADOLESCENTS WITH CONDUCT PROBLEMS AND VARYING LEVELS OF CALLOUS-UNE MOTIONAL TRAITS

Introduction

Children and adolescents with conduct problems constitute a heterogeneous group reflecting variability in the genetic, environmental, and neurobiological contributions to antisocial behavior (Viding et al., 2012a). It has been suggested that youths with both conduct problems and high levels of callous-unemotional traits comprise a distinct sub-group (Frick & Ellis, 1999; Frick & White, 2008) who are at particular risk for poor developmental outcomes (Frick, Cornell, Barry, Bodin, & Dane, 2003; Frick, Stickle, Dandreaux, Farrell, & Kimonis, 2005), including adult psychopathy (Frick, 2009). Adult psychopathy is characterized by antisocial behavior and a suite of cognitive and affective traits including shallow affect, lack of remorse and guilt, and impaired empathy (Hare, 1991), as well as functional and structural abnormalities in brain regions including the amygdala and orbitofrontal cortex (Blair, 2003a; Blair, 2005d; Blair, 2010). Adolescent conduct problems and high levels of callous-unemotional traits are thought to be developmental precursors to adult psychopathy (Frick, 2009), and because of the high financial and social burden on society, due to high rates of criminality, incarceration, and recidivism among psychopaths (Salekin, 2008), there has been a particular emphasis on understanding the neurobiological profile of at risk youths.
To this end, previous studies have investigated differences in brain morphology among at
juveniles at risk for psychopathy: Consistent with structural abnormalities found in adult
psychopaths (Weber, Habel, Amunts, & Schneider, 2008; Gregory et al., 2012; Pardini,
Erickson, Loeber, & Raine, 2013), volumetric studies measuring gray matter volume in boys
with conduct disorder (and therefore at greater risk for developing psychopathy as adults) have
found, relative to healthy controls, reduced volume in the amygdala (Huebner et al., 2008;
Sterzer et al., 2007; Fairchild et al., 2011; Wallace et al., 2013), prefrontal cortex (Huebner et al.,
2008; Fairchild et al., 2011), and insula (Sterzer et al., 2007; Fairchild et al., 2011), and reduced
amygdala and striatal volume has been found in girls with conduct disorder (Fairchild et al.,
2013).

These studies, however, are limited in their ability to disambiguate whether reductions in
gray matter volume are best accounted for by externalizing symptoms associated with conduct
disorder, such as acts of aggression and violence, or callous-unemotional traits. The importance
of disentangling these two variables is underscored by evidence that variability in levels of
callous-unemotional traits may correspond to distinct neurobiological profiles among youths
with conduct problems (Viding et al., 2012b; Sebastian et al., 2012), which has implications for
identifying the best treatments and interventions for youths with distinct subtypes of conduct
disorder (Viding et al., 2012a). However, externalizing behaviors and callous-unemotional traits
are highly correlated (Fontaine, McCrory, Boivin, Moffitt, & Viding, 2011), and their covariance
may cause statistical suppressor effects that make it difficult elucidate how each is related to
important outcome variables (Hicks & Patrick, 2006; Sebastian et al., 2012). Suppressor effects
can occur when two predictors that are correlated, such as externalizing behaviors and callous-
unemotional traits, have opposite associations with an outcome variable (Hicks & Patrick, 2006). Recent functional neuroimaging studies in youth with conduct problems have sought to account for suppressor effects, and found distinct activation patterns in the amygdala associated with externalizing behaviors and callous-unemotional traits (Viding et al., 2012b; Sebastian et al., 2012) and consistent with the results elaborated in Chapter III. While it remains unclear whether externalizing behaviors and callous-unemotional traits are associated with distinct patterns of structural abnormalities, there is some evidence this might be the case. Contrary to previously found group differences in which individuals with conduct problems had reduced gray matter volume compared to healthy controls (Huebner et al., 2008; Sterzer et al., 2007; Fairchild et al., 2011; Fairchild et al., 2013), a volumetric study in a community sample of boys with both elevated callous-unemotional traits and conduct problems actually found increased gray matter volume in the temporal lobes (and increased gray matter concentration in the medial orbitofrontal and anterior cingulate cortices) (De Brito et al., 2009). If externalizing behaviors and callous-unemotional traits are differentially related to gray matter in a way similar to their opposite relationships with activation patterns (Viding et al., 2012b; Sebastian et al., 2012) (i.e., one variable is associated with increased volume while the other is associated with decreased volume despite the two being highly correlated with each other), the discrepancies in the volumetric studies may reflect the relative severity of externalizing behaviors versus callous-unemotional traits among those with conduct problems in their samples.

To our knowledge, this is the first structural imaging study to investigate the unique contributions of externalizing behaviors and callous-unemotional traits on gray matter volume differences in a mixed gender sample of children and adolescents with conduct problems and
varying levels of callous-unemotional traits. We collected structural MRI data from healthy controls and youths with both conduct problems and callous-unemotional traits and used voxel-based morphometry (VBM) to measure gray matter volume. Multiple regression analysis was used to assess how callous-unemotional traits (controlling for externalizing behaviors) and externalizing behaviors (controlling for callous-unemotional traits) are each associated with gray matter volume.

Methods

Participants

Participants were 51 youths ages 10 to 17 recruited from the Washington, DC community via fliers, brochures, and advertisements. Written informed consent and assent were obtained from parents/guardians and participants, respectively, and children and parents completed a battery of assessments. All participants had an estimated full-scale IQ of at least 80 measured by the Kaufman Brief Intelligence Test-2 (K-BIT) (Kaufman, 1990) and reported no history of head trauma or neurological disorder. One healthy control was excluded due to use of psychotropic medication (specify) and data from 7 participants (2 healthy controls and 5 with conduct problems) were excluded due to motion artifacts in their anatomical scans. Qualified participants (n = 43) were 28 youths with conduct problems and 15 healthy controls. See Table 1 for participant characteristics.
Table 1

**Demographic and Clinical Characteristics of Participants with Conduct Problems and Healthy Controls**

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>Healthy Controls (n = 15)</th>
<th>Conduct Problems (n = 28)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic variables, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male : Female ratio</td>
<td>10 : 5</td>
<td>15 : 13</td>
<td>.52</td>
</tr>
<tr>
<td>Age</td>
<td>12.91 (2.39)</td>
<td>14.89 (2.37)</td>
<td>.02*</td>
</tr>
<tr>
<td>Cognitive intelligence</td>
<td>111.60 (3.94)</td>
<td>98.21 (1.76)</td>
<td>.01*</td>
</tr>
<tr>
<td>Behavioral measures, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child Behavioral Checklist</td>
<td>42.67 (9.35)</td>
<td>72.43 (4.86)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Inventory of Callous-Unemotional Traits</td>
<td>25.40 (6.88)</td>
<td>44.92 (8.14)</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

*Note.* Full-scale IQ from KBIT-2, Child Behavior Checklist scores are the age and gender standardized t-scores of externalizing behavior (items measuring aggression and rule-breaking), and the Inventory of Callous-Unemotional Traits scores is are derived from the maximum score on each item from the parent and youth versions. Asterisk (*) denotes significant groups differences at p < .05, two-tailed, measured with t-tests except for gender (Fisher’s exact test).
Assessment instruments

Parents completed The Strengths and Difficulties Questionnaire (SDQ) as a preliminary assessment of conduct problems (Goodman, 1997; Viding et al., 2012b). The SDQ is a 25-item measure of emotional symptoms, hyperactivity, peer problems, prosocial behavior, and conduct problems; a score ≥ 4 on the conduct problems scale signifies clinically significant conduct problems (Goodman, 1997). Parents also completed The Child Behavior Checklist (CBCL) (Achenbach, 1991), composed of empirically derived items selected to discriminate between clinically referred and typically developing samples (Jensen et al., 1996). An age and gender normalized t-score ≥ 65 on the externalizing behavior subscale of the CBCL signifies clinically significant externalizing behaviors (Achenbach, 1991) and was used as an estimate of conduct problems. Youths who met criteria for conduct problems on both the SDQ and CBCL were included in the conduct problems group. Healthy controls did not meet criteria for conduct problems on either measure.

The Inventory of Callous-Unemotional Traits (ICU) (Kimonis et al., 2008) is a 24-item instrument measuring callous-unemotional traits in youths. Participants and a parent separately rated each item using a 4-point scale. For each item, the highest numeric response given by either the youth or parent was summed to create a maximum total score (Jones et al., 2009; Sebastian et al., 2012).

Image acquisition

High-resolution T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) structural scans (TR = 1900 ms, TE = 5.52 ms, 1.03 mm voxels, 176 slices, 246 x
256 matrix, FOV = 250 mm) were acquired with a 3T Siemens Tim Trio scanner (Siemens Medical Solutions, Erlangen, Germany) and 8-channel phased-array head coil.

*Image analysis*

Anatomical scans were visually inspected for movement and other image artifacts; scans from 7 participants as mentioned above were excluded from analyses due to poor image quality. Data from 43 participants were pre-processed according to a customized pediatric workflow (Beal, Gracco, Brettschneider, Kroll, & De Nil, 2012) using VBM8 (http://dbm.neuro.uni-jena.de/vbm/) and in SPM8 (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (Version 7.11.1, Mathworks, Inc., Sherborn, MA). The Template-O-Matic Toolbox (Wilke, Holland, Altaye, & Gaser, 2008) and pediatric reference data from NIH study of normal brain development (http://www.bic.mni.mcgill.ca/nihpd/info) was used to create customized tissue probability maps and a study specific MNI template based on the age and gender of our sample. TI-weighted volumes were segmented into gray matter, white matter, and cerebrospinal fluid, and spatially normalized to the custom template using low dimensional standard SPM8 normalization procedures; this normalization approach is recommended by the VBM8 manual or pediatric samples of fewer than 50 (Kurth, Luders, & Gaser, 2010).

Resultant normalized, bias corrected images were visually inspected for accurate segmentation and normalization and the normalized, modulated non-linear gray matter images were assessed for sample homogeneity via covariance matrices and no outliers were identified. Finally, normalized, modulated non-linear gray matter images were smoothed with a 8mm full-width half-maximum filter and used for group level analyses.
Group level whole-brain and multiple regression analyses were conducted. Participant age and cognitive intelligence scores were included as covariates of no interest to account for group differences in these variables; and gender was included also included as a covariate of no interest to account for morphometric gender differences between boys and girls (Giedd, 2004). To investigate the associations between gray matter volume and our variables of interest (externalizing behaviors and callous-unemotional traits), regression analyses were conducted in both the full sample and separately for the participants with conduct problems; externalizing behaviors and callous-unemotional traits were simultaneous modeled as continuous variables to identify the unique contributions of each variable (Sebastian et al., 2012; Markon et al., 2011). A $p < .05$ cluster extent threshold with correction for non-sphericity was applied to resultant $t$-maps initially thresholded at $p < .001$ uncorrected and anatomical coordinates are reported in MNI space.

Results

Whole-Brain Analyses

In keeping with previous studies, whole-brain group comparisons were conducted including age, cognitive intelligence, and gender as covariates of no interest. Comparing healthy controls ($n = 15$) and all participants with conduct problems ($n = 28$), we found controls had greater gray matter volume in right parahippocampal gyrus/amygdala ($xyz = 12, -3, -20; k = 58$) and right cerebellum ($xyz = 56, -66, -30; k = 44$) and those with conduct problems had greater gray matter volume in the left postcentral gyrus ($xyz = -50, -24, 51; k = 132$).

Multiple Regression Analyses
Results of the multiple regression analysis in the full sample of both youths with conduct problems and healthy controls, including age, cognitive intelligence, and gender as covariates of no interest, indicated externalizing behaviors (accounting for callous-unemotional traits) were positively associated with gray matter volume in the left and right superior parietal areas including the precuneus and right middle frontal gyrus; no areas were negatively associated with externalizing behaviors. Callous-unemotional traits (accounting for externalizing behaviors) were positively associated with gray matter volume in the precentral gyrus and negatively associated with gray matter volume in the cerebellum (Figure 1). See Table 2 for all coordinates and their locations.
Figure 1. Results of a Regression Analysis in Youths With Conduct Problems. Regions positively associated with callous-unemotional traits after accounting for age, cognitive intelligence, gender, and externalizing behaviors. Height threshold $p < .001$ uncorrected; $p < .05$ cluster extent threshold with correction for non-sphericity.
Table 2

Regions of Activation Positively and Negatively Associated with Conduct Problems and Callous-Unemotional Traits in Youths With Conduct Problems and Healthy Controls

<table>
<thead>
<tr>
<th>Anatomical Regions</th>
<th>L / R</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>k_e</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive associations with externalizing behaviors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior frontal gyrus</td>
<td>R</td>
<td>-32</td>
<td>-67</td>
<td>-5</td>
<td>130</td>
<td>4.78</td>
</tr>
<tr>
<td>Superior parietal lobule</td>
<td>L</td>
<td>16</td>
<td>-79</td>
<td>56</td>
<td>168</td>
<td>4.70</td>
</tr>
<tr>
<td>Middle occipital gyrus</td>
<td>R</td>
<td>33</td>
<td>-85</td>
<td>25</td>
<td>354</td>
<td>3.94</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>R</td>
<td>40</td>
<td>58</td>
<td>-2</td>
<td>59</td>
<td>3.76</td>
</tr>
<tr>
<td>Middle cingulum</td>
<td>R</td>
<td>-16</td>
<td>-69</td>
<td>64</td>
<td>47</td>
<td>3.49</td>
</tr>
<tr>
<td>Superior parietal lobule</td>
<td>L</td>
<td>-27</td>
<td>-76</td>
<td>49</td>
<td>44</td>
<td>3.49</td>
</tr>
<tr>
<td><strong>Negative associations with externalizing behaviors</strong></td>
<td></td>
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<td>-</td>
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<tr>
<td><strong>Positive associations with callous-unemotional traits</strong></td>
<td></td>
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<tr>
<td>Postcentral gyrus</td>
<td>L</td>
<td>-44</td>
<td>-33</td>
<td>67</td>
<td>73</td>
<td>3.60</td>
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<tr>
<td><strong>Negative associations with callous-unemotional traits</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Cerebellum</td>
<td>L</td>
<td>-4</td>
<td>-42</td>
<td>-11</td>
<td>458</td>
<td>4.34</td>
</tr>
</tbody>
</table>

Note. Results with height threshold \( p < .001 \) uncorrected and \( p < .05 \) cluster extent threshold with correction for non-sphericity. Coordinates reported in MNI space.
When the multiple regression analysis was restricted to youths with conduct problems, we found externalizing behaviors were positively associated with gray matter volume in the right middle temporal gyrus extending into the inferior temporal gyrus and negatively associated with volume in the left and right posterior cingulate gyrus. Callous-unemotional traits were positively associated with gray matter volume in regions including the right amygdala, right inferior orbitofrontal cortex (BA47), a cluster in the right putamen extending into the caudate, right insula, and left and right posterior cingulate. Callous-unemotional traits were also negatively associated with gray matter volume in the left and right middle frontal gyrus. See Table 3 for all coordinates and their locations.
Table 3

Regions of Activation Positively and Negatively Associated with Conduct Problems and Callous-Unemotional Traits in Youths With Conduct Problems

<table>
<thead>
<tr>
<th>Anatomical Regions</th>
<th>L / R</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>k_c</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive associations with externalizing behaviors</strong></td>
<td></td>
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<td><strong>Positive associations with callous-unemotional traits</strong></td>
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Note. Results with height threshold $p < .001$ uncorrected and $p < .05$ cluster extent threshold with correction for non-sphericity. Coordinates reported in MNI space.
Discussion

In this study, we used VBM to assess gray matter volume differences in children and adolescents with conduct problems and healthy controls. First, a whole brain group analysis found that youths with conduct problems, compared to healthy controls, had reduced gray matter volume in the right amygdala. This is consistent with a number of previous volumetric studies (Huebner et al., 2008; Sterzer et al., 2007; Fairchild et al., 2011; Fairchild et al., 2013) and further evidence that amygdala abnormalities are an important feature of juvenile conduct problems (Marsh et al., 2008; Jones et al., 2009; White et al., 2012; Viding et al., 2012b).

Amygdala dysfunction in these individuals is thought to be related to attenuated responses to important socio-affective cues such as fearful facial expressions (Marsh et al., 2008; Jones et al., 2009; White et al., 2012; Viding et al., 2012b), which are thought to elicit empathy and reduce aggression (Blair, 2005d; Marsh & Ambady, 2007). Aberrant processing of these cues may be related to the antisocial behaviors common in youths with conduct problems and in the development of psychopathy in adulthood (Crowe & Blair, 2008; Blair, 2005d).

Importantly, the results of our multiple regression analysis provide clarification as to what features of juvenile conduct problems are related to documented reductions in amygdala volume. Because externalizing behaviors and callous-unemotional traits are often highly correlated (Fontaine et al., 2011), previous studies have failed to fully disentangle whether externalizing behaviors or callous-unemotional traits best account for these structural abnormalities. This is important because increasing evidence suggests that variability in callous-unemotional among youths with conduct problems may correspond to distinct subtypes with
different neurobiological profiles (Viding et al., 2012b; Sebastian et al., 2012), which is an important clinical considerations for treatments and interventions (Viding et al., 2012a).

Accounting for externalizing behaviors, age, cognitive intelligence, and gender, a whole-brain regression analysis restricted to the conduct problems group found gray matter volume in the amygdala was actually positively associated with callous-unemotional traits, which suggests that although overall amygdala volume is reduced in this group, components of the conduct problems phenotype other than the affective traits associated with adult psychopathy are contributing to reductions in volume. Interesting, callous-unemotional traits were also positively associated with volume in the orbitofrontal cortex, caudate, putamen, and insula, areas in which previous volumetric studies have found, like the amygdala, usually have reduced volume compared to healthy controls (Sterzer et al., 2007; Fairchild et al., 2011; Huebner et al., 2008). Because we did not find volumetric group differences in these regions, it is possible that other factors are contributing to overall volume decreases that counteract any volume increases attributed to callous-unemotional traits. This may also be why regression analysis in the entire sample combining both the conduct problems group and healthy controls did not yield the same results. Additionally, these findings underscore the importance of using regression analyses in concert with group analyses, which can obscure complex relationships between variables that have competing influences on structure and function.

There has been some previous evidence that externalizing behaviors are negatively correlated with gray matter volume in prefrontal cortex, insula, and limbic regions (Huebner et al., 2008; Sterzer et al., 2007; Fairchild et al., 2011), and although we did not find this relationship, our results are not altogether inconsistent with these findings. In order to account
for statistical suppressor effects, which can occur when two correlated variables exhibit opposite relationships with an outcome variable (Hicks & Patrick, 2006), we simultaneously modeled externalizing behaviors and callous-unemotional traits as continuous variables. In our model, shared variance between the two variables was likely better explained by callous-unemotional traits, even if externalizing behaviors were negatively correlated with gray matter volume in these regions. This suggests that the gray matter reductions in youths with conduct problems frequently found may be more related to the antisocial behavioral phenotype, and that the pathology of callous-unemotional traits may actually be associated with abnormalities related to increased gray matter, perhaps reflecting abnormal pruning during development (Gogtay & Thompson, 2010).

Our results should be interpreted in the context of several limitations and considerations. First, externalizing behaviors and callous-unemotional traits were not measured with clinical assessments. Although previous studies had similar results using clinical (Marsh et al., 2008; White et al., 2012) and research (Jones et al., 2009; Viding et al., 2012b) assessments, it is unclear whether our findings will generalize to individuals with clinically-defined conduct disorder. Additionally, youths with conduct problems were significantly younger and had cognitive intelligence scores compared to healthy controls, but age and cognitive intelligence were included as covariates of no interest in all of our analyses.

Nevertheless, to our knowledge this is the first study to investigate how gray matter volume differences in a mixed gender sample of youths with conduct problems specifically relate to variation in the severity of externalizing behaviors and callous-unemotional traits. Given increasing importance of fully characterizing the neurocognitive profiles of youths with conduct...
problems in order to develop better risk assessments and effective treatments (Viding et al., 2012a; Frick & Moffitt, 2010; Frick, 2012), our study is an important contribution towards resolving the distinct neural correlates associated with different sub-types of affected children and adolescents.
This dissertation investigated the behavioral and neural basis of processing affective facial expressions in two different populations: individuals with autism spectrum disorders (ASD) and children and adolescents with conduct problems. Chapter II detailed a meta-analysis of explicit face-emotion recognition in children and adults with ASD, integrating data from 1,545 participants across 43 studies. The results provided strong evidence that individuals with ASD have generalized deficits in recognizing emotional facial expressions and that the development of these recognition abilities progresses along a developmental trajectory that differs from typical individuals. Chapter III also investigated face-emotion processing, using behavioral measures and functional magnetic resonance imaging (fMRI) data collected during an implicit face-emotion processing task that was completed by youths with conduct problems and callous-unemotional traits. The results of a multiple regression analysis indicated amygdala responses to fearful facial expressions were differentially associated with externalizing behaviors and callous-unemotional traits, whereby externalizing behaviors were positively associated with amygdala activity and callous-unemotional traits were negatively associated with amygdala activity. Moreover, amygdala responses to fearful expressions were found to mediate the relationship between callous-unemotional traits and proactive aggression. Chapter IV further explored the neural basis of externalizing behaviors and callous-unemotional traits in children and adolescents with conduct problems. Voxel-based morphometry (VBM) was used to assess
gray matter volume differences in youths with conduct problems and healthy controls. Individuals with conduct problems, relative to controls, had reduced gray matter volume in the amygdala; within this group, gray matter volume in the amygdala, orbitofrontal cortex, caudate, putamen, and insula was positively associated with callous-unemotional traits. The current chapter will integrate Chapters II-IV within the framework of face-emotion processing in ASD and psychopathy and discuss associated deficits in empathy.

ASD and psychopathy are distinct developmental disorders that have overlapping features, most notably impaired facial affect recognition and deficits in empathy (Blair, 2008; Nichols, 2001). These similarities suggest the two disorders may share some common abnormalities in the underlying neural circuitry that supports social cognition. However, the type of dysfunctions associated with each disorder are distinct: As demonstrated in Chapter II, ASD is associated with generalized deficits in face-emotion recognition for multiple expressions, and, as noted previously, is also associated with diminished cognitive empathy (Baron-Cohen et al., 1985). By contrast, psychopathy is associated with poor recognition of fearful facial expressions (Marsh & Blair, 2008) and deficits in affective empathy (Blair, 2005a). The differences in how face-emotion recognition and empathic deficits manifest indicate that while there may be some neural commonalities between the two, there are necessarily major differences in how any shared abnormalities develop, progress, and impact behavior.

To understand this, one first has to consider the typical development of the neural circuitry that underlies face-emotion recognition. Infants are born with an incipient face-emotion processing network that serves as the building blocks for the distributed and highly interconnected network that later develops. Core regions include the superior temporal sulcus
(STS), lateral fusiform gyrus (FFA), orbitofrontal cortex (OFC), and the amygdala. These areas have basic connections with each other that are rapidly refined through tuning and pruning as the network undergoes experience-dependent plasticity during the first year of life. Plasticity and fine-tuning continues throughout development (Leppanen & Nelson, 2009; Leppänen, 2011).

Anatomically and functionally central to this network is the amygdala, which seems to be a particularly important hub and abnormalities of which may have an outsized role in network dysfunction. The amygdala is a bilateral, subcortical structure located in the temporal lobes. It is comprised of anatomically and functionally distinct subnuclei: The lateral and basolateral nuclei receive sensory information from the thalamus and visual cortex, which is relayed to the central nucleus of the amygdala; the central nucleus has widespread projections to the neocortex and subcortical areas, including reciprocal connections with the lateral fusiform gyrus and orbitofrontal cortex (Whalen & Phelps, 2009). Historically, functions of the amygdala have been linked to physiological and behavioral responses to fear-inducing or fear-related stimuli. Both human and animal studies have found the amygdala mediates responses to fearful stimuli (e.g. shocks and predators), such as changes in heart rate and skin conductance, freezing, flight, approach, and avoidance (LeDoux, 2003), particularly via the central nucleus which projects information about fear-relevant stimuli to subcortical centers that coordinate these responses (Whalen & Phelps, 2009), and is also crucial for fear conditioning (Maren, 2001) through connections with the hippocampus (Whalen & Phelps, 2009). However, functions of the amygdala are not just relegated to the fear domain. It is also involved in orienting visual attention and helps direct eye gaze to relevant stimuli through connections with the superior colliculi and visual cortex (Whalen & Phelps, 2009), and is thought to be involved in several dimensions of
social cognition (Adolphs, 2010), including empathy (Blair, 2008), via its extensive connections throughout the cortex (Whalen & Phelps, 2009).

Given the vast structural and functional connectivity of the amygdala, it is not surprising that it is considered both an important component of the circuitry underlying face-emotion recognition in general (Adolphs, 2002), and plays an outsized role in fear recognition specifically (Fusar-Poli et al., 2009). And because network connections mature via experience-dependent plasticity during development (Leppanen & Nelson, 2009), how face-emotion recognition deficits manifest as a function of amygdala abnormalities is necessarily related to both primary amygdala dysfunction and any resultant secondary dysfunction in interconnected regions. It follows that variation in the precise nature of the amygdala abnormalities, and the presence of any other network aberrations or vulnerabilities, would result in distinct developmental pathologies with specific functional consequences, which might be the case for ASD and psychopathy.

The generalized deficits associated with ASD described in Chapter II indicate widespread dysfunction across multiple structures involved in processing affective facial expressions, widespread dysfunction in how these regions communicate, or dysfunction in key regions that contribute to widespread, downstream abnormalities. Because face-emotion recognition involves visual, cognitive, and affective component processes (Adolphs, 2002) supported by a distributed network including visual, limbic, temporal, tempoparietal, and prefrontal regions (Adolphs, 2002; Haxby et al., 2002; Vuilleumier & Pourtois, 2007; Fusar-Poli et al., 2009), a number of areas and their connections could be atypical in ASD and contribute to generalized face-emotion recognition deficits. Indeed, neuroimaging studies of face-emotion recognition in ASD have
found diffusely distributed abnormal activation patterns and altered functional connectivity throughout this network (Harms et al., 2010): Findings include reduced activation in the cerebellum (Critchley et al., 2000), visual (Deeley et al., 2007), and frontal (Loveland, Steinberg, Pearson, Mansour, & Reddoch, 2008; Ogai et al., 2003; Dapretto et al., 2006; Greimel et al., 2010; Hall, Szechtm, & Nahmias, 2003) regions; increased activation in the amygdala (Dalton et al., 2005; Monk et al., 2010), parietal cortex (Dapretto et al., 2006; Hubl et al., 2003; Wang et al., 2004), superior temporal sulcus and anterior cingulate (Ashwin, Baron-Cohen, Wheelwright, O’Riordan, & Bullmore, 2007; Hall et al., 2003; Pelphrey, Morris, McCarthy, & LaBar, 2007); and altered functional and effective connectivity (Monk et al., 2010; Wicker et al., 2008).

Owing to the major interconnectivity of these regions and the reciprocal tuning they undergo during development, there may be more central or specific abnormalities that contribute to the pervasive dysfunction in the face-emotion processing network. Previous research has indicated the amygdala as a potential dysfunctional hub associated with ASD to such an extent that it has led to ‘The Amygdala Theory of Autism’ (Baron-Cohen et al., 2000). Studies have found morphological abnormalities (Sparks et al., 2002; Schumann et al., 2004; Mosconi et al., 2009; Aylward et al., 1999; Nacewicz et al., 2006; Schumann & Amaral, 2005) and atypical activation patterns compared to controls across a myriad of neuroimaging tasks (Castelli, Frith, Happé, & Frith, 2002; Gervais et al., 2004; Dalton et al., 2005; Ashwin et al., 2007; Grelotti et al., 2005; Pelphrey, Morris, & McCarthy, 2005). Additionally, the characteristic behavior of individuals with ASD to avoid eye contact and fail to attend to the relevant features of stimuli further supports amygdala dysfunction (Dalton et al., 2005; Nacewicz et al., 2006; Pelphrey et al., 2002).
In contrast to ASD, investigations of the behavioral and neural basis of face-emotion recognition deficits implicated in psychopathy have found more narrowly focused results. One of the most robust features of psychopathy is a profound and selective deficit in recognizing fearful expressions while recognition of other expressions remains intact (Marsh & Blair, 2008). Such an isolated deficit suggests the neural circuitry underlying general facial affect recognition is largely preserved, and that dysfunction is localized to areas specifically involved in processing fear-related stimuli or within circuitry that does not preclude the recognition of other expressions. As such, previous studies have found amygdala abnormalities are also a prominent feature in psychopathy, evidenced by reduced neural responses to fearful expressions and morphological differences relative to healthy controls (Ermer et al., 2011; Kiehl et al., 2001; Anderson & Kiehl, 2012; Blair, 2005b; Blair, 2010; Boccardi et al., 2011; Yang, Raine, Narr, Colletti, & Toga, 2009; Yang, Raine, Colletti, Toga, & Narr, 2010; Craig et al., 2009; Motzkin, Newman, Kiehl, & Koenigs, 2011). Fear recognition deficits and amygdala abnormalities have also been found in studies of youths with conduct problems (Marsh et al., 2008; Jones et al., 2009; White et al., 2012; Viding et al., 2012b; Huebner et al., 2008; Sterzer et al., 2007; Fairchild et al., 2011; Fairchild et al., 2013), who, particularly if they have both juvenile conduct problems and high levels of callous-unemotional traits, are at increased risk for developing adult psychopathy (Frick, 2009). These findings are supported by the studies detailed in Chapters III and IV that found callous-unemotional traits were negatively associated with amygdala responses to fearful expressions and positively associated with amygdala gray matter volume. The results constitute further evidence that amygdala dysfunction is a central feature of psychopathy; that this dysfunction is apparent during childhood and adolescence; and that
structural abnormalities and attenuated responses to fearful expressions are distinctly related to callous-unemotional traits, the developmental precursors of the affective deficits that characterize psychopathy.

Suppositions that amygdala dysfunction in psychopathy is related to specific impairments in the recognition of fearful expressions may seem counterfactual given that the amygdala is part of the circuitry involved in recognition of all expressions (Leppänen, 2011) and has been implicated in the generalized face-emotion recognition deficits in ASD (Sasson, 2006). How might amygdala dysfunction be a feature of both ASD and psychopathy, and be simultaneously related to the seemingly mutually exclusive deficits that characterize these disorders? Because network connections mature via experience-dependent plasticity during development (Leppanen & Nelson, 2009), how face-emotion recognition deficits manifest as a function of the amygdala is necessarily related to both the primary amygdala dysfunction and any resultant secondary dysfunction in interconnected regions. Primary amygdala dysfunction could result from a number of abnormalities which could have distinct affects in the functions of the amygdala, such as atypical numbers of neurons, proper function of cell transport systems, and aberrant connections between sub-nuclei. Additionally, issues with receptor density or receptor expression in key neurotransmitters including oxytocin, vasopressin, and serotonin could affect important behaviors such as aggression and empathy (Bartz et al., 2010; Beitchman et al., 2012; De Dreu, 2012; Poulin, Holman, & Buffone, 2012). Therefore, variation in the precise nature of the amygdala abnormalities, and the presence of any other network aberrations or vulnerabilities, would result in distinct developmental pathologies with specific functional consequences, such as those in ASD and psychopathy.
In infants with ASD, there is strong evidence that the amygdala is not properly functioning from birth: The amygdala-dependent behavior of spontaneous gaze to the eyes of others is markedly reduced or absent (Jones & Klin, 2013) coupled with gray matter enlargement that persists for the first two years of life (Mosconi et al., 2009). This nascent amygdala dysfunction could initiate a developmental cascade resulting in generalized face-emotion recognition deficits and diffuse abnormalities in underlying circuitry. One potential mechanism for these impairments is disrupted reciprocal interaction between the amygdala and lateral fusiform gyrus (Schultz et al., 2003; Dziobek et al., 2010; Dalton et al., 2005), whereby the amygdala fails to orient visual attention to relevant facial features (Dawson et al., 2004; Pelphrey et al., 2002) and in turn the fusiform gyrus is poorly tuned (Jiang et al., 2006). Dysfunction begets dysfunction and there is likely a snowballing effect whereby regions directly and indirectly connected with the amygdala undergo atypical development, which is supported by continued structural and functional amygdala abnormalities evident throughout the lifespan and the myriad dysfunctional brain regions associated with processing facial affect. The results from Chapter II that found age-related deficits in face-emotion recognition increase over time also supports this account of an altered developmental trajectory.

Because ASD and psychopathy are characterized by different recognition deficits (general deficits in ASD and fear-specific deficits in psychopathy), early amygdala dysfunction in psychopathy most likely follows a different pathology. Similar to ASD, there is evidence for the presence of structural and functional amygdala abnormalities early in development, and as indicated in Chapters III and IV dysfunction is specifically related to the severity of callous-unemotional traits that correspond to the affective components of psychopathy. But unlike ASD,
evidence that psychopathy is associated with poor eye contact and failure to visually orient to faces is only poorly supported (Dadds et al., 2006; Dadds, El Masry, Wimalaweera, & Guastella, 2008), and certainly not the well-documented and robust phenotype characteristic of ASD (American Psychiatric Association, 2000). Moreover, psychopathy is associated with widespread problems across multiple dimensions of fear processing, such as fear-learning (Lopez, Poy, Patrick, & Molto, 2012; Fairchild et al., 2010) and autonomic physiological responses to fear-invoking stimuli (Arnett, Howland, Smith, & Newman, 1993; Marsh et al., 2011b; Fairchild et al., 2010), which is not true of ASD. This suggests amygdala abnormalities associated with psychopathy are fundamentally different from those associated with ASD and emotion recognition deficits result from a mechanism other than altered amygdala-fusiform connectivity that exclusively targets fear recognition yet accommodates development of the expression-invariant processes of face-emotion recognition. Because recognition for all expressions other than fear is unaffected in psychopathy, amygdala abnormalities are not affecting the general development of the face-emotion recognition network but become evident only when the functions of the amygdala specifically for fear processing are required. This is in line with speculations that the basolateral nucleus of amygdala may be underactive while the central nucleus is functioning at average or above average levels (Moul, Killcross, & Dadds, 2012) and evidence for altered connectivity between the amygdala and orbitofrontal cortex (Blair, 2003a; Marsh et al., 2011a; Iidaka et al., 2001; Passamonti et al., 2012), which would be consistent with specific impairments in recognizing fearful expressions and poor affective regulation characteristic of psychopathy (Blair, 2005b).
Amygdala abnormalities and the distinct face-emotion recognition deficits they are associated with may also be related to the differential empathy deficits associated with ASD and psychopathy. Impairments in facial affect recognition, whether general or emotion-specific, can have profound repercussions for social reciprocity. The ability to recognize and respond appropriately to emotional facial expressions is a critical aspect of non-verbal communication and often co-occurs with deficits in important social competencies such as empathy (Blair, 2008). Empathy is a multi-factorial construct that is broadly described as the understanding and sharing of the experiences and emotions of others (Eisenberg & Strayer, 1987; De Waal, 2008). Despite a huge body of work investigating empathy, the term “empathy” still lacks a formal, consensus-driven definition, and the component processes of empathy are still somewhat debatable (Bernhardt & Singer, 2012; Blair, 2008). Some recent conceptualizations of empathy have emphasized two complementary yet separate systems, cognitive and affective, that are thought to be distinct processes with dissociable neural correlates (Vollm et al., 2006; Blair, 2008; Shamay-Tsoory, 2011; Raz et al., 2014).

Cognitive empathy, sometimes referred to as theory of mind, involves understanding the perspective of another person, adopting his or her point of view, and making inferences about that person’s psychological state (Baron-Cohen, 1997; Shamay-Tsoory, 2011; Frith & Singer, 2008). Theory of mind itself has cognitive and affective components, whereby cognitive theory of mind is making inferences about another’s beliefs while affective theory of mind is making inferences about another’s emotions. Importantly, affective theory of mind is not the same as affective empathy; it is a cognitive process involving mentalizing about the emotions of others (Shamay-Tsoory, 2011). Both components of theory of mind involve top-down inferences about
the mental state of another by assigning beliefs, thoughts, and motivations to that person. Brain regions involved in these processes include the medial prefrontal cortex, superior temporal sulcus, and temporo-parietal junction, and precuneus (Bzdok et al., 2012; Dodell-Feder, Koster-Hale, Bedny, & Saxe, 2011; Raz et al., 2014).

Affective empathy, on the other hand, is characterized by the ability to sense and share another’s emotional state; it involves emotion recognition and emotional contagion, an automatic state-matching reaction whereby the observer adopts the emotional feelings of another (Shamay-Tsoory, 2011). It is considered an automatic, bottom-up process and relies on neural circuitry involved in both self-experience and the perception of similar states in others. Regions including the anterior insula, part of the inferior frontal gyrus, middle anterior cingulate, and precuneus are thought to comprise an affective empathy network that supports these processes (Lamm, Decety, & Singer, 2011; Bruneau, Pluta, & Saxe, 2012; Raz et al., 2014).

It has been suggested that the relative balance between cognitive and emotional empathy characterizes an individual’s overall empathic ability (Cox et al., 2012), and asymmetrical deficits of the two systems are implicated in ASD and psychopathy: ASD is associated with impairments in cognitive but not affective empathy and, conversely, psychopathy is associated with impairments in affective empathy while cognitive empathy remains intact (Blair, 2008; Nichols, 2001).

Deficits in cognitive empathy, or theory of mind, are a central feature of ASD. Both facial affect recognition and cognitive empathy are important components of social behavior, but how the two are related in ASD remains unclear. Although the neural substrates of facial affect recognition have a weak correspondence with theory of mind circuitry, is possible that early
disruptions in the experience-dependent processes that correspond to atypical face-emotion processing also disrupt theory of mind development. This is supported by evidence that amygdala damage early in development is related to impaired theory of mind abilities (Shaw et al., 2004), and given the diffuse and extensive connections between the amygdala and other cortical and subcortical areas, cascading detrimental effects stemming from amygdala abnormalities could hinder theory of mind development. And considering ASD is associated with recognition deficits for all emotions, as evidenced in Chapter II, it makes sense that individuals would have difficulty attributing thoughts and beliefs to others if they are unable to reliably categorize a person’s emotional state even at a broad level. In other words, poor tuning of the amygdala-fusiform pathway could hinder the ability to form a mental representation of the emotional states of others and therefore preclude making cognitive inferences and taking that person’s perspective.

In psychopathy, evidence suggests deficits in affective empathy stem from the same amygdala dysfunction implicated in aberrant facial affect recognition—insensitivity to the distress cues of others. It is thought that in typical individuals, observation of distress cues like fearful expressions elicits empathy via emotional contagion, which produces a shared emotional state (Shamay-Tsoory, 2011), and may lead to sympathetic concern (De Waal, 2008; Nichols, 2001), the motivation to help others (Eisenberg, 2007), and reduced aggression (Dawel et al., 2012; Marsh & Blair, 2008; Sylvers et al., 2011). But in psychopathy, impaired recognition of distress cues impedes emotional contagion, which in turn disrupts affective empathy (De Waal, 2008; Nichols, 2001) and mechanisms that inhibit aggression. This is consistent with evidence that the affective empathy system in particular requires amygdala involvement (Raz et al., 2014;
and the results of the mediation analysis described in Chapter III that found attenuated amygdala responses to fearful expressions mediate the relationship between callous-unemotional traits and proactive aggression.

Comparing ASD and psychopathy, it is evident that the differential impairments in empathy are fundamentally related to the differential face-emotion recognition deficits characteristic of the two disorders. The neural circuitry involved in both empathy and processing affective facial expressions are interactive (Raz et al., 2014), particularly via the amygdala and regions connected to the amygdala (Vollm et al., 2006). The pathology of ASD and psychopathy are likely related to core but distinct amygdala abnormalities that have downstream consequences and contribute to atypical development. In ASD, amygdala dysfunction is associated with eye gaze deficits that may impede proper tuning of amygdala-fusiform connections, which in turn impedes proper development of recognition for all facial expressions. Consequently, this may affect theory of mind abilities that require intact mentalization of another’s emotional state. By contrast, amygdala dysfunction in psychopathy is related to a profound deficit in fear processing across domains that disparately inhibits the development of recognition of fearful expressions and prevents the emotional state matching necessary for affective empathy.

Conclusions

The aim of this dissertation was clarify and refine our understanding of the behavioral and neural basis of social cognition by comparing two disorders of face-emotion recognition and empathy, ASD and psychopathy. Each study is a discrete and important element towards this
goal. The work in Chapter II resolves major inconsistencies in previous studies of face-emotion recognition in ASD and provides strong evidence of face-emotion recognition deficits for all expressions, the development of which follow a different age-related trajectory than normal. This knowledge is crucial towards understanding dysfunction in networks necessary for processing affective expression and how these impairments might affect other areas of social cognition. Chapters III and IV add important knowledge towards characterizing the development of psychopathy and how the amygdala relates to the affective phenotype characteristic of the disorder. Chapter III specifically links callous-unemotional traits to hypoactivity in the amygdala in response to fearful expressions and that this response mediates aggression. Chapter IV also found a strong relationship between amygdala morphology and callous-unemotional traits, providing further evidence there are core amygdala abnormalities associated with psychopathy that are present early in development. These studies address specific knowledge gaps that, taken together, can enhance our understanding of the development of both typical and atypical social cognition.
REFERENCES


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