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Amygdalar Abnormalities and Social Cognitive Correlates in Youth at Clinical High Risk for Psychosis

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Amygdalar Abnormalities and Social Cognitive Correlates in Youth at Clinical High Risk for Psychosis

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An abstract of a thesis submitted to the Faculty of the
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Abstract

Amygdalar Abnormalities and Social Cognitive Correlates in Youth at Clinical High for Psychosis

By: Allison Macdonald

Structural brain abnormalities have been implicated in the pathogenesis of psychosis, however the extent to which these abnormalities represent neurodegenerative changes associated with illness duration or represent early vulnerability markers remains unclear. Accumulating evidence suggests that social cognitive impairments and dysfunction of the corresponding brain circuits may precede illness onset and be at the core of psychosis pathology. Thus, the nature and role of volumetric abnormalities in the amygdala and amygdala-prefrontal regions, as well as their clinical correlates are of great interest. The present study examined amygdalar and amgydala: prefrontal ratio volumes, and their association with facial emotion recognition deficits, in youth at clinical high risk for psychosis. Structural magnetic resonance imaging and the Penn-40 Facial Emotion Recognition Task were used to assess neuroanatomical volumes and facial emotion recognition performance in youth at clinical high risk (n=254) and controls (n=122). Results showed that CHR youth had larger amygdalar and amygdala:prefrontal ratio volumes, as well as worse facial emotion recognition performance, compared to controls. This observed enlargement was specific to the left amygdala and was more pronounced in CHR youth who had been medicated with antipsychotics. In the CHR – Unmedicated youth, the ratio volume was negatively associated with facial emotion recognition performance and was a better predictor than the amygdalar and prefrontal volumes alone. These finding suggest that enlarged amygdalar volumes may characterize the prodrome and that the balance between the size of the amygdala and prefrontal cortex may contribute to facial emotion recognition deficits.

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Schizophrenia is a complex, heterogeneous disorder that affects approximately 1% of the population worldwide (Jablensky, 1997). The presentation of behavioral disturbances and cognitive deficits leads to a chronic course of illness marked by significant functional and social impairment. Despite extensive research efforts, the cause and etiological determinants remain largely unknown. While antipsychotics and psychosocial interventions can bring about some improvement, relapse is common even among well-treated individuals and difficulties in functioning persist (Addington et al., 2003). In the past decade, there has been an increased interest in the period of functional decline that precedes the clinical onset of psychosis. This period, referred to as the prodrome, can last from months to several years and is thought to provide an optimal time for preventive intervention (Addington & Heinssen, 2012). Characterizing the phenomenology and identifying biomarkers in this period has become a top priority and has the potential to elucidate neurobiological aspects of the disorder.

It is well accepted that schizophrenia is associated with structural brain abnormalities (Lawrie & Abukmeil, 1998; Shenton, Dickey, Frumin, & McCarley, 2001; Liddle & Pantelis, 2003). However the nature, course, and functional significance of these abnormalities in the emergence of the disorder remain unclear. More specifically, it is unclear whether volumetric abnormalities represent neurodegenerative changes associated with illness duration or whether they represent early vulnerability markers for psychosis. Recent evidence suggests that anatomical alterations may precede illness onset and denote underlying risk, however further work is needed (Pantelis et al. 2003; Knowles & Sharma, 2004). The extent to which these alterations are associated with clinical characteristics also remains unknown. However, identification of structural abnormalities and their clinical correlates in the psychosis prodrome may shed light on developmental mechanisms of the disorder. .

Structural imaging work in the schizophrenia-spectrum has focused primarily on gray matter volume, prefrontal, striatal, and hippocampal regions (Lawrie & Abukmeil, 1998; Shenton, Dickey, Frumin, & McCarley, 2001; Liddle & Pantelis, 2003). The results have been consistent in showing volumetric reductions in the cortex, especially prefrontal cortex, and the hippocampus in both at-risk samples and patients diagnosed with psychosis. While the amygdala has been strongly implicated in a number of other psychiatric conditions, it has received less attention in schizophrenia models. However, the amygdala is a prime candidate for pathology given its anatomical characteristics as well as its role in social cognitive and emotional processes. While hallucinations and delusions often represent the public face of schizophrenia, difficulties with social interactions and emotional processing are among the most pervasive and disabling deficits in the disorder (APA, 2000). Accumulating evidence suggests that social-emotional impairments and dysfunction of the corresponding brain circuits may be at the core of schizophrenia pathology (Ciompi, 1998; Fett et al., 2011; Penn, Combs, & Mohammed, 2001; Aleman & Kahn, 2005).

To date, no imaging studies have looked at the anatomic integrity of the amygdala or its relationship with social cognitive abilities in the prodome. Thus, the goals of the present study are to 1.) determine whether volumetric abnormalities in the amygdala are present in CHR youth and 2.) to determine whether these abnormalities are associated with social cognitive deficits in facial emotion recognition.

Amygdala as Candidate for Pathology

There are a number of reasons to suggest that amygdalar dysfunction is involved in schizophrenia-spectrum disorders. The anatomical characteristics and functional roles of the amygdala lend themselves to models of psychosis pathology. For example, the amygdala is more

susceptible to insults than other brain regions and therefore may be more vulnerable to the pathophysiological processes associated with psychosis (Cannon et al. 2003). Consistent with neurodevelopmental conceptualizations of the disorder, morphometric alterations could result from anomalies in pregnancy, synaptic pruning, abnormal brain maturation, the adverse effects of stress, and other environmental factors (Pantelis et al. 2005). These subtle amygdalar abnormalities could remain clinically dormant until exacerbated by maturational processes in the adolescent years, precipitating the onset of psychotic symptoms and social deficits. The amygdala's protracted development may also increase its susceptibility to alterations. Cross-sectional MRI studies indicate that typically the developing amygdala increases in volume by 40% from 5 years of age to late adolescence, with many key cortical connections strengthening during adolescence (Giedd, 1997; Giedd, Snell, & Lange, 1996, Ostby et al., 2009; Schumann et al., 2004). This large window for insults and anomalies leaves the amygdala particularly vulnerable to volumetric alterations. Further, brain development does not follow a single global pattern, but instead undergoes asynchronous periods of change (Smith, Chein, & Steinberg, 2013). In contrast to the amygdala, other brain regions (e g., prefrontal cortex) are characterized by volumetric decline in the adolescent period. The differential maturation patterns in the structure and function of brain regions leads to periods of pronounced imbalance and vulnerability for psychiatric illness.

The complex multinuclear structure of the amygdala exhibits structural and functional connectivity with a number of subcortical and cortical areas, making it one of the most connected brain regions (Ochsner, 2008). As a result, even subtle amygdalar abnormalities have the potential to produce widespread neural dysfunction. Among these connections are dense and direct projections with the prefrontal cortex, a region most consistently associated with

schizophrenia pathology (Molina, Sanz, Sarramea, Beniton, & Paloma, 2004; Gur et al. 2004; Lipska & Wenberger, 2002). Moreover, the emergence of prodromal symptoms and social deficits in adolescence parallels the period in which neural connections between the amygdala and prefrontal cortex are established (Benes, 1998; Walker and Bollini, 2002) and the amygdala-prefrontal circuitry becomes fine-tuned (Fair et al. 2007, Kelly et al., 2009). Consequently, structural abnormalities of the amygdala could lead to critical disruptions in the development of this circuitry, resulting in the emergence of emotion processing deficits and symptoms (Pantelis et al., 2003).

Finally, the well-established presence of social cognitive and emotional processing deficits in schizophrenia-spectrum disorders is suggestive of amygdalar dysfunction. Lesion, animal, and functional imaging studies have consistently implicated the amygdala in emotional processing (Baxter and Murray, 2002; Adolphs, 2001; Gur et al., 2002a; LeDoux, 2000; Yaniv et al., 2004; Adolphs et al., 1998; Winston et al., 2002; Rosenfeld et al., 2011). While the amygdala is most commonly associated with fear and sadness recognition, functional imaging has shown it to respond to a range of emotions (e.g., happiness, surprise and neutral) of both negative and positive valence (Adolphs, 1995; Fusar-Poli, Placentino, Carletti, et al., 2009; Edwards, Jackson, & Pattison, 2002; Pomarol-Clotet et al., 2010).

The structural integrity of the amygdala has also been shown to influence emotional processing (Gur et al. 2002a, Adolphs et al. 1999, Adolphs et al. 1994). For example, work with primates has shown that discrete lesions to the amygdala produce weakened fear perception and social response (Amaral, 2003; Hamman et al. 1996). Meanwhile, impairment in facial emotion recognition has been documented in humans who have suffered bilateral amygdalar damage (Adolphs et al., 1994, 1995, 1999; Sato et al., 2002, Graham, Devinsky & LaBar, 2007).

Although amygdalar lesions are not equivalent to reduced amygdalar volume, the findings are consistent with the possibility that reduced amygdalar volume may contribute to aberrant emotional processing. While volumetric amygdalar reductions and lesions seem to attenuate emotional perception, volumetric amygdalar enlargements appear to amplify it. This amplification is commonly observed in other psychiatric disorders associated with volumetric amygdalar enlargements, including affective disorders (Frodl et al., 2002; Lange & Irle, 2004; Weniger et al., 2006), anxiety disorders (Kim et al., 2010) and post-traumatic stress disorder (Karl et al., 2006; Atmaca et al., 2008; Woon and Hedges, 2008). These classes of disorders are characterized by heightened and often inaccurate emotional perception, particularly of fear and sadness. However, the relationship between amygdala structure and emotional processing is not restricted to pathological conditions but seems to exist in the general population as well (Zhang et al., 2012). For example, van der Plas and colleagues (2011) found that amygdala volume was positively associated with fear perception in healthy adolescent females. Taken together, these findings suggest that amygdalar volumetric abnormalities, in either direction, may influence emotional processing and result in inaccurate perception.

Amygdalar Abnormalities in the Schizophrenia-Spectrum

Reports of amygdalar volume abnormalities across the schizophrenia-spectrum have been variable. Schizophrenia patients have most consistently shown amygdalar volume reductions by 6-10% compared to controls (Wright et al., 2000; Lawrie & Abukmeil, 1998, Nelson et al., 1998) and there is evidence of a stronger reduction on the left side (HulshoffPol et al., 2001; Lawrie et al., 2003). However, there have also been reports of amygdalar enlargment (Velkoulis et al. , 2006) as well reports of no differences (Rajarethinam et al., 2001) These mixed findings suggest that age of onset, phase of illness, and illness duration may influence volumetric measurements,

as studies greatly vary in their sample composition and characteristics. Even within simliar phases of illness, age of onset can lead to different findings. For example, first-episode patients in late adolescence have shown abnormal amygdalar enlargements (Velkoulis et al., 2006), while first-episode patients in their late twenties have shown amygdalar reductions (Joyal et al., 2003; Witthaus et al., 2009). These findings highlight the importance of examining the developmental trajectory of the amygdala across the disease process, as degenerative effects associated with illness duration, as well as antipsychotics, may contribute to amygdalar volumetric reductions in later phases of illness. To better understand the role and morphometric status of the amygdala in psychosis, it will be important to examine amygdalar volume in the prodromal phase.

Amygdalar volumes in high-risk samples have only been examined in a small number of studies. In adolescents with schizotypal personality disorder, amygdalar volumes were significantly reduced (Hendren et al., 1995; Yeo et al., 1997; Suzuki et al., 2005). In addition, group differences were more prominent for the left amygdala, a lateralization effect often observed in schizophrenia patient populations (Shenton et al., 2001; Hulshoff Pol et al., 2001). Reduced amygdala volumes have also been documented in young offspring of schizophrenia patients (Keshaven et al., 1997). This evidence suggests structural abnormalities of the amygdala are present in high-risk individuals prior to illness onset. However, the sample sizes of these studies have been small and the risk-groups have primarily included individuals who were not experiencing prodromal symptoms and therefore may be less likely to develop a psychotic disorder. Further investigation is needed with clinical-high risk individuals to establish whether amygdalar abnormalities are neurobiological markers in the prodromal period, or whether these abnormalities develop progressively over the course of illness. Following this, it is also of

interest to investigate how these abnormalities may be related to clinical characteristics, such as social cognitive deficits.

Facial Emotion Recognition in the Schizophrenia-Spectrum

Given the amygdala's central role in emotional processing, it is likely that the social cognitive impairments observed in the schizophrenia-spectrum are indicative of amygdalar dysfunction. One basic component of social cognitive functioning is facial emotion recognition, which involves recognizing and discriminating amongst distinct facial emotional expressions. Facial emotion recognition plays a significant role in social interactions as the face is the most prominent social stimuli and communicates information about one's emotional state and intentions (Gothard et al., 2007). The ability to accurately perceive emotional information is critical to normal social interactions and serves as a building block for higher-level emotional processing and social behaviors. Impairments in these bottom-up processes may generate impairments in more top-down cognitive processes leading to misguided social responses such as withdrawal, suspiciousness, and paranoia (Phillips et al., 2008; Taylor et al.,2005). Additionally, facial emotion recognition deficits appear to be more pronounced than general facial discrimination deficits in schizophrenia patients (Feinberg, Rifkin, Schaffer, & Walker, 1986). Thus, impairments in facial emotion recognition processes may be a primary source of the social-emotional dysfunction observed in schizophrenia.

Facial emotion recognition deficits in both discrimination and identification have been documented across the schizophrenia-spectrum (Irani, Seligman, Kamath, Kohler, & Gur, 2012; Penn et al., 1997; Edwards, Jackson, & Pattison, 2002; Hellewell & Whittaker, 1998; Mandal, Pandey, & Prasad, 1998; Morrison, Bellack, & Mueser, 1988; for review see Kohler et al. 2010). These deficits appear stable across illness (Addington et al., 2006; Pinkham et al., 2007; Green et

al., 2011) and are independent of depressive symptoms (Kohler & Martin, 2006) and general intelligence (Edwards, 2001).

Findings suggest that facial emotion recognition deficits are not limited to individuals with schizophrenia, but may be more broadly related to psychosis vulnerability (Phillips & Siedman, 2008). In CHR youth the literature is limited and the results have been mixed. Pinkham (2007) did not detect differences between CHR individuals and control individuals on facial emotion recognition tasks. However, the authors note a small sample size and suggest the particular emotion recognition task used (Facial Emotion Identification Test) may not pick up on subtle deficits. Conversely, both Addington et al. (2011) and Amminger et al. (2012) found that CHR individuals performed significantly worse than controls, and similar to psychotic patients, on facial emotion recognition tasks.

Furthermore, genetic-high risk (GHR) youth, who are typically symptom free but may demonstrate deficits conferred by genetic liability, have also been found to perform worse on facial emotion recognition tasks (Bediou et al., 2007; Eacks et al., 2010; Kee, Horan, Mintz, & Green, 2004). Specifically, Eacks et al. (2010) found that GHR individuals were more likely to over attribute emotion to neutral faces and predominantly misinterpreted such faces as negatively valenced, a finding consistent with the schizophrenia literature (Penn, Corrigan, Bentall, Racenstein et al., 1997; Edwards, Jackson, & Pattison, 2002). Similar findings have also been reported in individuals with varying levels of schizotypy, or psychosis proneness (Germine & Hooker, 2011; Brown & Cohen, 2010; Kerns, 2006). Germine & Hooker (2011) found that schizotypy scores were positively associated with facial emotion recognition deficits. Taken together, these results indicate that facial emotion recognition ability may vary with degree of psychosis vulnerability.

Amygdala:Prefrontal Ratios

As noted above, brain regions vary in their developmental trajectories. During normal adolescent development there is an increase in the volume of the amygdala and some other limbic structures but a decrease in cortical volume. At the functional level, cortical activation appears to be less pronounced during this period than activation of limbic structures. Consequently, it has been suggested that some of the characteristic behaviors associated with adolescence (e g., risk taking, emotional lability) and the increased risk for psychopathology are a reflection of the discrepancy between the limbic and cortical developmental courses. The balance of limbic to cortical maturation may be most discrepant during this period and influence important behavioral and cognitive processes (Casey, Jones, & Hare, 2008).

Recent evidence suggests that examining the morphological relationship between the amygdala and other subcortical and cortical regions may be a better predictor of outcomes than the morphological status of the amygdala alone. Recent work has examined the structural relations of amygdalar-cortical and amygdalar-hippocampal areas in relation to memory performance (Gerristen et al. 2012), anxiety (MacMillan et al. 2003), emotion regulation (Albaugh et al. 2013) and emotional responses (Suzuki et al. 20130) in both clinical and healthy samples. Gerristen and colleagues (2012) found that while larger amygdalar volumes and smaller hippocampal volumes were both positively associated with negative memory bias in a healthy sample, the ratio between the two volumes showed a much stronger association. Similarly, MacMillan et al. (2003) found that in a pediatric population the volumetric ratio between amygdalar and hippocampal volume showed a stronger association with anxiety severity than either region alone. These results suggest that the balance between the sizes of the two regions may be more informative than the absolute volumes of the individual brain regions.

It has also been suggested that relationships between cortical and subcortical volumes, particularly negative relationships, reflect patterns of functional connectivity between antagonistic brain areas (Gong, He, Chen, & Evans, 2012). That is, brain regions that have functionally reciprocal relationships show negative associations in structural volume. For example, Albaugh and colleagues (2013) found that prefrontal cortices were reciprocally related with the amygdala at the functional level, and that the nature of this relationship was detected at the structural level as well. The authors suggest that structural volumetric ratio between these two regions may recapitulate functional connectivity and be an informative marker of dysregulated emotional behavior. Taken together, recent work suggests that ratio volumes have the potential to highlight meaningful imbalances at the structural level, which may reflect concomitant disruptions at the functional level.

Given the anatomical connections between the amygdala and the prefrontal areas, the prefrontal cortices are positioned to play an integral role in the regulating of amygdalar activity (Ghashghaei et al., 2007; Ray & Zald, 2012). Functional magnetic resonance imaging studies have consistently demonstrated top-down modulation of amygdalar activity by the prefrontal cortices (Banks et al., 2007; Drabant et al., 2009; Oschner et al., 2004). The reciprocal relationship between the amygdala and prefrontal cortex strongly suggests the need to investigate these brain regions together, rather than studying them separately. Like the amygdala, volumetric alterations of the prefrontal cortex have been reported in schizophrenia patients (Hirayasu et al., 2001). Consequently, the relationship between amygdalar and prefrontal volume, and its relationship to emotion perception is also of great interest. While amygdalar abnormalities alone may contribute to emotion perception deficits, the balance of the amygdala with the prefrontal cortex may be a better predictor of the phenomena.

Present Study

The present study aims to examine the nature of amygdalar and amygdalar:prefrontal ratio volumetric alterations in youth at clinical high risk for psychosis. As mentioned above, examining these neuroanatomical alterations in the prodrome has the potential to highlight vulnerability markers and neural substrates related to disease pathology. Additionally, the association between these anatomical alterations and facial emotion recognition performance will be tested.

1. Based on past findings across the schizophrenia-spectrum, it is hypothesized that CHR youth will have altered amygdalar and amygdala:prefrontal ratio volumes compared to controls. It is predicted that CHR youth will show reduced cortical volume relative to controls, but similar or enlarged amygdala volume, thus yielding a larger ratio of amygdala to prefrontal cortical volume.
2. It is hypothesized that amygdalar and amygdalar:prefrontal ratio volume will be negatively associated with facial emotion recognition performance. Such that greater volumetric imbalance, as indexed by a larger ratio volume, will be related to worse performance.

Method

Participants

The present sample is drawn from participants originally recruited for the North American Prodromal Longitudinal Study (NAPLS) II, a multi-site longitudinal study of clinical high-risk youth. Recruitment was accomplished through newspaper, bus, and online announcements containing descriptions of prodromal symptoms in lay terms (i.e. unusual ideas, perceptual abnormalities, increased suspicious, social withdrawal). Normal controls were recruited through

the same outlets but with an alternate announcement. Participants were excluded from NAPLS-II if at baseline they 1.) met DSM-IV criteria for an Axis I psychotic disorder; 2.) had experienced a significant head injury; 3.) met substance dependence criteria within the past 6 months; 4.) had a neurological disorder; or 5.) had a Full Scale IQ <70. Additionally, control participants were excluded if they had a first-degree relative with a current or past psychotic disorder, or met prodromal criteria

The clinical high-risk group (CHR) includes 254 individuals (156 males, 98 females) ranging from 12 to 35 years of age (*M*=19.31, *SD*=4.09 years). This group is 57.1% Caucasian, 14.7% Black, 8.4% Asian, 1.2% Middle Eastern, 4.8% Hispanic, 1.6% Native American and 12.3% Interracial. The control group includes 122 participants (71 males, 53 females) between the ages of 12 and 34 (*M*=19.17, *SD*=4.61 years). This group was 57.2% Caucasian, 13.9% Black, 5.7% Asian, 0.08% Middle Eastern, 5.7% Hispanic, 2.5% Native American and 11.5% Interracial.

Measures

Facial Emotion Recognition. Facial emotion recognition was assessed using the Penn Emotion Recognition Test-40, a facial emotion recognition paradigm commonly employed in schizophrenia research. The Penn Emotion Recognition Test-40 is a computer-based test of emotion recognition that randomly presents emotional (happy, sad, angry, or fearful) and nonemotional (neutral) faces to participants and asks them to choose from the emotional label that best suits the displayed face. A forced-choice format is used during the tests where participants have to choose among the labels “happy”, “sad”, “angry”, “fearful” or “neutral” for the faces presented. The race and gender of the faces are randomly dispersed throughout the task. Key performance metrics from this paradigm include the accuracy with which participants identify emotional and neutral faces, as well as the speed at which participants provide their

responses, in the form of reaction time. In the present study the accuracy score (total # correct) was used to index facial emotion recognition performance. Previous research has shown this emotion recognition paradigm to be capable of discriminating between schizophrenia patients and healthy controls (Kohler, Turner, Bilker, Brensinger et al. 2003).

Prodromal Symptomatology. The Structured Interview for Prodromal Syndromes (SIPS) was administered to assess the presence of one or more prodromal syndromes. Data obtained from the SIPS is used to rate the severity of relevant symptoms on the SIPS scale: 0 = *absent*, 1 = *questionably present*, 2 = *mild*, 3 = *moderate*, 4 = *moderately severe*, 5 = *severe but not psychotic*, and 6 = *severe, psychotic*. The SIPS is composed of four symptom domains; 1.) *Positive* (e.g., unusual thought content/ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities, and disorganized communication); 2.) *Negative* (e.g., social isolation, avolition, decreased expression of emotion, decreased experience of emotions and self, decreased ideational richness, and deterioration of role functioning), 3.) *Disorganized* (e.g., odd behavior of appearance, bizarre thinking, trouble with focus and attention, and impairment in personal hygiene or social attentiveness), and 4.) *General* (e.g., difficulty related to sleep disturbance, dysphoric mood, motor disturbances, and impaired tolerance to normal stress). A prodromal syndrome was diagnosed if an individual 1.) manifested a rating of 6 on a positive symptom in the past 3 months, but did not meet criteria for a psychotic disorder (i.e., *Brief Intermittent Psychotic Syndrome*; BIPS); 2.) received at least one rating of 3, 4, or 5 on a positive symptom (i.e., *Attenuated Positive Symptom Syndrome*; APSS), 3.) had a first degree relative with a nonaffective psychotic disorder and had experienced a functional decline over the past year (i.e., Genetic Risk and Deterioration Syndrome; GRDS), or 4.) were <19 years of age at baseline and met diagnostic criteria for Schizotypal Personality Disorder (SPD). CHR individuals can meet

criteria for more than one prodromal syndrome.

MRI Image Acquisition and Processing. High-resolution scans were acquired from 3T scanners (5 Siemens, 3 General Electric) with standardized MRI protocols. All scans were acquired in the sagittal plane with a 1mm x 1mm in-plane resolution and 1.2mm slice thickness. Siemens scanners used an MPRAGE sequence with a 256 (axial) x 240 (sagittal) x 176 (coronal) mm field of view, TR/TE/TI=2300/2.91/900ms and a 9 degree flip angle, while GE scanners used an IR-SPGR sequence with a 26cm field of view, TR/TE/TI=7.0/minimum full/400ms and an 8 degree flip angle. Following the standard steps of the FSL VBM package (version 4.1.4), brain images were extracted from all scans and were subsequently segmented into gray matter, white matter, and CSF images. All gray matter images were registered to an ICBM brain template using non-linear registration and were averaged to generate a study specific gray matter template. All gray matter images were then non-linearly registered to the above-generated study-specific template to minimize inter-subject anatomical variation. Gray matter volumetric information was preserved by adjusting image intensity according to the magnitude of local contraction or expansion during registration. The registered gray matter images were smoothed by applying a Gaussian kernel (sigma=3 mm) prior to statistical analysis. The FSL First package was used to extract subcortical structures. Two-stage linear registrations were applied to bring the subcortical regions of individual scans into alignment with the MNI 152 template. Next, based on a large training dataset of manually labeled brain images, automated segmentation was performed to segment 15 subcortical structures (i.e., brainstem and left and right thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and accumbens) by integrating shaping modeling into a Bayesian framework. Volumes of subcortical structures were calculated. Within and between-site reliabilities are reported in Cannon et al. 2013. Gray matter density in

prefrontal and temporal cortical surfaces as well as for volumes of subcortical structures achieved reliability in the good-excellent range.

Procedures

Study procedures took place at the eight NAPLS locations (Emory, Yale, Harvard, UNC-Chapel Hill, UCLA, UCSD, Hillside Hospital, and University of Calgary). An initial screening interview was conducted to ensure the individuals met prodromal criteria on the SIPS, or qualified as a control. Once study inclusion was established, participants were administered a baseline battery of clinical measures, neuropsychological tests, and social cognitive tasks, including the Penn Emotion Recognition Test. A structural MRI scan was conducted on the second day of baseline data collection.

Analytic Strategy

All analyses were performed using IBM SPSS 21.0. Analysis of variance (ANOVA) was used to test group differences in demographic characteristics and medication status. Linear regression was used to examine group differences in brain regions of interest and facial emotion performance. Consistent with the neuroimaging literature, the effects of age, sex, and intracranial volume (ICV) were controlled for in all neuroanatomical analyses. To understand the relationship between brain volume and facial emotion recognition performance bivariate correlations were examined. Linear regression was then used to determine whether the relationship between brain regions of interest and facial emotion performance differed by group. The additive effects of amygdalar and prefrontal volume, as well as the ratio of these two regions (amygdala:prefrontal), were also tested. As described above, the ratio is intended to index the relative morphologic status and, thereby, the potential functional consequences of the relative influence of these two regions. Effects with a p-value less than 0.05 were considered significant.

Results

Demographic Characteristics

In this sample, the CHR group had a larger number of males than females (Table 1), which is typical of CHR samples. The groups did not significantly differ in age or race. Antipsychotic use was restricted to the CHR group and characterized 27.4% of the sample. Consistent with the literature ICV were significantly correlated with the brain regions of interest across both groups and was subsequently included as covariates in all analyses (Table 2). As shown in Table 2, age was negatively correlated with prefrontal volume and there was a trend towards positive correlation with amygdala volume, consistent with the developmental trajectories of these two regions (Sturman & Moghaddam, 2011). However, the correlation between age and amygdala volume was only significant in the CHR group. Consistent with the literature, men had larger volumes across all brain indices. After controlling for ICV, there were still sex differences in total amygdalar volume ($\beta = -0.19, p < .01$) and amygdala:prefrontal ratio volume ($\beta = -0.18, p < .01$), but not in prefrontal volume. Facial emotion recognition performance did not differ by sex.

Group Differences in Brain Volumes and Facial Emotion Performance

A graphical depiction of mean differences can be found in Figure 2. The total amygdalar volume for the CHR group was 9% larger than the control group [$F(1,372)=29.31, p < .01$]. When the amygdalar hemispheres were examined separately, group differences were only observed in the left amygdala [$F(1,372)= 4.73, p =. 03$]. There were no group differences in prefrontal cortex volume. However, the amygdalar: prefrontal ratio volume was 4% larger in the CHR group relative to controls [$F(1,372)= 21.24, p < 0.01$]. Additionally, the CHR group had worse facial emotion recognition performance [$F(1,372)=9.27, p < .01$].

Given the potential relation of antipsychotic use with brain volumes, group differences between medicated and unmedicated individuals were examined within the CHR group (Figure 3). The total amygdalar volume in the CHR-Medicated group was 5% larger than the CHR-Unmedicated group [$F(1,246)=4.02$, $p= 0.03$, $\eta^2=0.02$]. When the amygdalar hemispheres were examined separately, there were no significant group differences. There were also no group differences in prefrontal cortex volume. However, the amygdalar:prefrontal ratio volume was 6% larger in CHR-Medicated individuals relative to CHR-Unmedicated individuals [$F(1,245)=5.61$, $p= 0.02$, $\eta^2=0.02$]. There were no significant group differences in facial emotion recognition performance between the two CHR groups. When CHR-Medicated individuals were removed from the CHR sample, there were no longer significant volumetric brain differences between the CHR group and the controls. However, the remaining CHR-Unmedicated individuals still had higher mean amygdalar volumes relative to controls. The CHR-Medicated [$F(1,228)=8.12$, $p <.01$, $\eta^2= 0.03$] and CHR-Unmedicated [$F(1,359)=4.38$, $p= .04$, $\eta^2= 0.01$] groups both had worse facial emotion recognition performance than controls but did not significantly differ from one another.

Exploratory analyses were conducted to further investigate the CHR group differences observed in the antipsychotic users. Analysis of variance (ANOVA) was used to examine CHR group differences in prodromal symptom severity. The CHR- Medicated group had higher mean scores across all symptoms domains (positive, negative, disorganized, and general) and were significantly higher than the CHR-Unmedicated group on negative symptoms [$F(1,330)=7.12$, $p < .01$, $\eta^2 = 0.02$] and disorganized symptoms [$F(1,330)=16.75$, $p < 0.01$, $\eta^2= 0.04$].

Association Between Brain Volumes and Facial Emotion Recognition Performance

Bivariate correlations were computed between brain volumes and the facial emotion recognition measures for each group (Table 3). In the CHR-Unmedicated group larger left amygdala volume, prefrontal volume, and the amygdala:prefrontal ratio was associated with worse facial emotion recognition. These relationships were not significant in the corresponding correlations for the CHR-Medicated and control groups.

Group differences in the relationship between brain volumes and facial emotion recognition performance were examined further with multiple regressions within each clinical status group (Table 4). In each regression analysis three models were tested, with facial emotion recognition performance as the dependent variable. In the first block age, sex, and ICV were entered. In the second block, total amygdala volumes and prefrontal cortex volume were entered. Finally, in the third block, the amygdala/prefrontal cortex ratio volume was entered.

The first regression model tested whether the control variables - age, sex, and ICV - predicted total facial emotion performance. The overall effect of all three variables on total performance was only significant for the CHR- Unmedicated group, accounting for 6% of the variance in total performance (R^2=0.06, p= 0.02). Of the three predictors only age was a significant (β = -0.23, $p < 0.01$). The second regression model tested whether total amygdala volume and prefrontal volume predicted facial emotion recognition performance, while holding constant the control variables in model one. Neither predictor accounted for a significant amount of variance in performance in any of the clinical status groups. Finally, the third regression model tested whether the amygdala:prefrontal ratio predicted total performance, while controlling for the predictors in models 1 and 2. Model three was significant only for the CHR-

Unmedicated group, accounting for 10% of the variance in performance ($R^2 = 0.10$, $p < 0.01$). The ratio was a significant predictor ($\beta = 0.18$, $p = 0.02$).

Discussion

In the present study we investigated whether CHR youth exhibited volumetric alterations of the amygdala and the amygdala:prefrontal ratio, and whether these volumetric alterations were related to facial emotion recognition deficits. Indeed, we found that CHR youth had larger amygdalar and amygdala:prefrontal ratio volumes, as well as worse facial emotion recognition performance, compared to controls. This observed enlargement was specific to the left amygdala and was more pronounced in CHR youth who had been medicated with antipsychotics. In the CHR – Unmedicated youth, there was a negative relationship between amygdalar/prefrontal ratio and facial emotion recognition performance. Interestingly, the ratio volume was a better predictor of performance than the amygdalar and prefrontal volumes alone. Our results suggest that in these CHR youth facial emotion recognition performance is not simply associated with larger amygdala volumes and smaller prefrontal cortex volumes separately, but that the balance between the sizes of these two structures is of importance.

Volumetric Brain Differences in CHR Youth

Our findings of enlarged amygdalar volumes in CHR youth are an important contribution to the current literature. To date, it has been unclear whether brain abnormalities observed in schizophrenia represent neurodegenerative changes associated with illness duration, or whether they represent early vulnerability markers for the disorder. By examining structural brain volumes in clinical high-risk youth we are able to better delineate this issue. The present findings suggest that amygdalar enlargement may characterize the prodromal period. Although

speculative, it is possible that this morphological enlargement results from pathophysiological processes associated with psychosis risk and may contribute to the clinical manifestation of the syndrome.

There are a number of mechanisms that could account for amygdalar enlargement in CHR youth that are consistent with current conceptualizations of the disorder. Genetic factors that affect postnatal neurodevelopment and cellular processes are among the potential candidates. Accumulating evidence suggests that the COMT, PRODH, DGCR8 and ZDHHC8 genes are involved in the pathological processes of schizophrenia (Drew et al., 2011; Mukai et al., 2004; Gogos & Gerber, 2006). These particular genes, which are expressed in brain tissue, are involved in neuronal proliferation, migration, and synaptic organization. As a result, even small variations in these genes have the potential to disrupt multiple aspects of neurobiological development and, in concert with other environmental and genomic influences, bias neural circuitry towards dysfunction (Maynard et al. 2003). This subset of genes is also associated with 22q.11.2 deletion syndrome, a chromosomal microdeletion condition associated with a high risk for schizophrenia (Gothelf et al. 2007a). In fact, 22q11.2 DS is one of the most powerful known risk factors for the development of schizophrenia and given its well-characterized genetic basis, provides a unique opportunity to identify genes and neurodevelopmental mechanisms associated with schizophrenia (Baker et al. 2011). Interestingly, enlarged amygdalar volumes have been reported in 22q.11.2 DS youth, highlighting the potential of these genetic factors to contribute to both risk for psychosis and aberrant amygdalar development.

Enlarged amygdalar volumes may also result from disruptions in neuronal pruning. Adolescence is a period of substantial cortical reorganization that involves programmed synaptic pruning. As a result, even a subtle anomaly in the timing or magnitude of typical maturational

processes could have a significant impact on brain function. While schizophrenia is often associated with exaggerated synaptic pruning of cortical areas, incomplete pruning in subcortical regions such as the amygdala could lead to an enlarged amygdalar volume and imbalance with other brain regions.

These anomalies in maturational processes may also act in concert with other psychosocial factors such as environmental stress. Increased stress exposure and HPA dysregulation have been consistently implicated in schizophrenia pathology (Walker, Mittal, & Tessner, 2008; Ryan, Sharifi, Condren, & Thakore, 2004). In the amygdala, cortisol increases dendritic arborization of the primary neurons resulting in increased amygdalar volume (Vyas et al., 2002; Pawlak et al., 2003; Cordero et al., 2005; Holzel et al., 2010). Additionally, the structural plasticity induced by stress appears to be less reversible than in other areas such as the hippocampus (Vyas et al., 2004). Taking the developmental trajectory into account, it is possible that hypertrophy and increased volume in the amygdala may occur in the prodromal period in response to stress – but may ultimately result in premature volume reductions due to excitotoxic processes. Such a developmental pattern is commonly observed in the depression literature in which larger amygdalar volumes are observed in first depressive episode populations compared to both controls and recurrent episode patient populations (Frodel., 2003; Lange & Irle, 2004). Although speculative, this pattern might also help unify the current literature and explain the volumetric amygdalar reductions often reported in chronic schizophrenia patient populations (Lawrie & Abukmeil, 1998; Wright et al., 2000). Increased amygdalar volume in CHR youth is also consistent with findings in depressed and anxious youth (Wenigeret al., 2006; Kim et al., 2010; Frondl et al., 2008). This is perhaps unsurprising given that depression and anxiety are common symptoms in the prodromal period and likely result from overlapping neurobiological processes.

Notably, our analyses showed that the amygdalar enlargement in CHR was specific to the left side. This is consistent with volumetric findings across the schizophrenia-spectrum, in which alterations in amygdalar volume were more prominent on the left. This hemispheric difference also compliments the lateralization effect observed in fMRI studies with emotion recognition paradigms (Baas et al., 2004, Glascher & Adolphs, 2003; Wright & Liu, 2006). These studies show increased activation in the left amygdala, relative to the right, in emotion processing tasks involving both positive and negative stimuli (Killgore & Yurgelun-Tood 2001). Left amydala activation has also been implicated in more sustained cognitive appraisals of emotional stimuli (Glascher & Adolphs, 2003). To date, there is a dearth of fMRI studies with CHR youth, however studies have shown that schizophrenia patients have elevated amygdala activity during passive viewing of emotional human faces compared to controls (Holt et al. 2006). It is possible that increased activation of the amygdala in CHR youth may precipitate experience-dependent neuronal modeling resulting in morphometric enlargements of the amygdala and concomitant imbalance with other subcortical and cortical regions. This amygdalar hyperexcitability, coupled with inadequate prefrontal control, could result in dysfunctional emotion processing.

We were also interested in the morphological relationship and balance between the amygdala and prefrontal cortex. While we cannot draw direct inferences about functionality from structural measures, accumulating research demonstrates that a number of anatomical networks in the brain can be identified by studying the structural relationships between subcortical and cortical regions (He et al., 2007; Zielinski et al., 2010). For example, ratios of brain regional volumes have been associated with memory bias (Gerristen et al., 2012), anxiety symptoms (MacMillan et al., 2003), and emotional responsivity (Suzuki et al. 2013). Additionally, it has been proposed that studying the structural relationship between the cortex and the amygdala can provide insight into

the functional relationship between the two regions. Patterns of functional connectivity, particularly between antagonistic brain regions, have been recapitulated by structural volumetric ratios (Gong et al., 2012). For example, Albaugh et al. 2013 found that the relationship between cortical volume and amygdalar volume reflected the functional reciprocity observed between the two regions during resting-state fMRI. Our study detected larger amygdalar/prefrontal ratios in CHR youth relative to controls. Although speculative, this observed imbalance may denote altered amygdala and prefrontal interactions whereby an overactive amygdala is not sufficiently regulated by the prefrontal cortex. Interestingly, a recent preliminary study with a subset of CHR youth taken from this sample, suggested an altered age-related trajectory of amygdala-prefrontal circuitry. While controls showed increasing PFC activation and decreasing amygdala activation with increasing age, CHR youth showed the opposite trajectory (Gee et al., 2012). In normative developmental there a shift to stronger top-down modulation of amygdalar activity as the connections between the amygdala and prefrontal cortex become strengthened in adolescence and early adulthood. These findings suggest that the relationship between prefrontal cortex and the amygdala may be altered in the developmental course of CHR youth.

Our findings regarding the increased amygdalar volume of CHR-Medicated youth relative to CHR-Unmedicated youth (and controls) raises two interesting possibilities. The first is that antipsychotics increase amygdalar volume. While some data suggests that antipsychotic use associated with gray matter decline (Ho et al., 2011), there is little research on the effects of this class of drugs on subcortical regions such as the amygdala. The second possibility is that the behavioral symptoms associated with increased amygdalar volume in adolescents (ex. anxiety, irritability, disinhibition, impulsivity) are more likely to elicit antipsychotic prescriptions. Exploratory analyses examining the relationship between medication status and symptoms

severity found significantly increased disorganized symptom severity. The disorganized symptoms domain includes odd behavior, bizarre thinking, and trouble with attention; symptoms that would likely increase the probability of being prescribed an antipsychotic in disturbed youth. Related to this, it is possible that individuals on antipsychotics represent a more severe subset of CHR youth. Medication status may thus serve as an index of severity and risk, which we see reflected in more severe pathophysiological processes and characteristics, such as altered brain volumes. Interestingly, exploratory analyses revealed that medication status was associated with more severe symptoms lending support to this possibility.

Amygdalar Volume and Facial Emotion Recognition Deficits in CHR Youth

Our results also show that in CHR-Unmedicated youth there is a negative association between the amygdala:prefrontal ratio and facial emotion recognition performance. Specifically, the amygdala:prefronal ratio was a better predictor than either brain region alone, suggesting that the imbalance between these two regions may have functional significance. While ratio variables with structural MRI data have been used less frequently, these measures may capture meaningful imbalances that relate to pathology. A number of studies have found that volumetric ratios of brain regions that vary in developmental course and function are more informative than either measure alone (Whitwell., 2012; Suzuki et al., 2013; Albaugh et al., 2013; Gerritsen et al., 2012). More specific to schizophrenia-spectrum disorders, Gur and colleagues (2004) found that alternations in frontal:amygdalar ratios were associated with severity of negative symptoms in male patients with psychosis such that decreased frontal:amygdalar ratio volumes (driven by larger amygdalar volumes) were associated with greater symptom severity. This association was stronger for the ratio than either region alone. Similarly, our results suggest that in these CHR youth facial emotion recognition performance is not simply associated with larger amygdala

volumes and smaller prefrontal cortex volumes separately, but with the balance between the sizes of these two structures. This is consistent with findings of reduced connectivity between amgydala and prefrontal regions in schizophrenia (Hoptman et al., 2010).

It is somewhat surprising that the association between amygdala:prefrontal volumes and facial emotion recognition was not observed in CHR – Medicated individuals given their pronounced morphological enlargements and performance deficits. One possibility is that antipsychotic medication actually improves facial emotion recognition performance. As suggested by others, abnormalities in dopamine transmission are thought to interfere with the amygdala's ability to assign the correct emotional salience to stimuli (Laviolette, 2007; Kapur et al., 2003). Antipsychotics block dopamine receptors and decrease dopamine transmission, which may lead to the attenuation of aberrant salience assignment (Kapur, Mizrahi, & Li, 2005). Consequently, antipsychotic use in the CHR-Medicated youth may have attenuated their emotional recognition deficits, making the amygdala:prefrontal ratio volumes less predictive. The lack of association between amygdala:prefrontal ratios and performance in controls may be due to the limited variability in the facial emotion recognition performance scores.

Strengths & Limitations

There are several notable strengths of the present study. To date, this is the largest sample of youth at clinical-high risk for psychosis. As a result, there was sufficient statistical power to detect small effects. The neuroimaging literature for schizophrenia-spectrum disorders has been limited by small sample sizes, which have likely contributed to the inconsistency of the findings. However, the present study provides ample power to reliably detect group differences in structural alterations. The reliability of neuroanatomical measurements across sites is a crucial aspect of power in multisite neuroimaging designs and is often modest. In the current study,

within-and between-site reliabilities of 0.95 or greater were achieved for gray matter density in prefrontal and temporal cortical surfaces as well as for volumes of subcortical structures (see Cannon et al. 2013). Additionally, the current sample represents the first half of the participants from the larger NAPLS II study. As a result, these findings can be replicated in the second half of the sample.

Several factors should be considered when interpreting our results. In the present study the amygdala and prefrontal cortex were treated as single functional units. The amygdala, however, is comprised of many discrete subnuclei, each with distinct patterns of connectivity. Similarly, the prefrontal cortex is comprised of regions with differential functions and connections. Future methods of reliably segmenting the amygdala into separate functional and structural units (*e.g.*, basolateral and central nuclei) may illuminate more specific neural substrates. It should also be noted that the effect sizes for the volumetric alterations were small. While even subtle differences in morphology can have significant implications for brain functioning, future work is needed to determine the functional relevance of these subtle volumetric alterations. Additionally, the present study employs a cross-sectional design that does not allow conclusions to be drawn about whether neuroanatomical alterations are predictive of conversion to psychosis. In regards to facial emotion recognition performance, it is important to note that there was no control task to determine whether the impairment was specific to emotions or was more generalized. In addition, the present study only examined one modality of emotion recognition (facial) and therefore generalizations about general emotion processing abilities cannot be made.

Conclusions

The examination of morphometric brain abnormalities and their clinical correlates in the psychosis prodrome provides a unique opportunity to identify etiological mechanisms

contributing to the pathogenesis of schizophrenia. The present study found that amygdalar and amygdalar:prefrontal volumetric ratios are altered in CHR youth and may underlie some of the emotional-social deficits observed in the prodrome. The amygdala and its relationship with prefrontal regions have received less attention in the schizophrenia literature, but may represent an important candidate of pathology. The findings also highlight the value of examining the volumetric ratio between brain regions, which may be more informative than measurements of individual brain regions alone.

To our knowledge, this is the first study to link amygdalar volumetric characteristics to facial emotion recognition impairments in the prodrome. Further work should investigate additional relationships between amygdala:prefrontal ratios and clinical characteristics, particularly in regards to symptomatology. It will also be important to determine whether prodromal amygdalar enlargement and ratio size represent specific vulnerability markers of schizophrenia, or whether they serve as nonspecific markers of general psychopathology. Utilizing longitudinal conversion data will help elucidate the specificity of this marker. Future investigations with fMRI technology will also help clarify the functional significance of these subtle morphometric abnormalities.

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Table 1

Demographic Characteristics

Variable		CHR (n = 254)	Control (n = 122)
Age (Mean ± SD)		19.31 ± 4.09	19.17 ± 4.61
Sex (n, %)*	Male	156 (61.4%)	71 (57.2%)
	Female	98 (38.6%)	53 (42.7%)
Race (n, %)	Caucasian	144 (57.1%)	73 (59.8%)
	Black	37 (14.7%)	17 (13.9%)
	Asian	21 (8.4%)	7 (5.7%)
	Middle Eastern	3 (1.2%)	1 (0.8%)
	Hispanic	12 (4.8%)	7 (5.7%)
	Native American	4 (1.6%)	3 (2.5%)
	Interracial	10 (12.3%)	14 (11.5%)
Antipsychotic Medication Status (n, %)***	Baseline Use	47 (18.5%)	0 (0%)
	Lifetime Use	24 (9.4%)	0 (0%)

*$p < .05$, **$p < .01$, ***$p < .001$

Table 2

Summary of Intercorrelations for Demographic Variables, Regions of Interest, and Facial Emotion Recognition Performance by Group.

CHR

	Variable	1	2	3	4	5	6	7
1.	Left amygdala							
2.	Right amygdala	.51**						
3.	Total amygdala	.85**	.88**					
4.	Prefrontal cortex	-.15	-.04	-.10				
5.	Amygdala:Prefrontal	.81**	.80**	.93**	-.5**			
6.	FER Performance	-.15*	-.09	-.13*	.06	-.14*		
7.	Age	.17**	.11	.16*	-.37**	.27**	-.13*	
8.	ICV	.41**	.43**	.48**	.21**	.35**	-.02	-.03

Controls

	Variable	1	2	3	4	5	6	7
1.	Left amygdala							
2.	Right amygdala	.48**						
3.	Total amygdala	.82**	.89**					
4.	Prefrontal cortex	.01	-.04	-.02				
5.	Amygdala:Prefrontal	.75**	.83**	.92**	-.4**			
6.	FER Performance	.07	-.03	.01	.05	.00		
7.	Age	-.01	.12	.06	-.26**	.16	.17*	
8.	ICV	.37**	.27**	.36**	.19*	.26**	.21*	-.02

Note. CHR (n=238) and Controls (n=119). FER= Facial Emotion Recognition.
*$p < .05$, **$p < .01$

Table 3

Summary of Intercorrelations for Demographic Variables, Regions of Interest, and Facial Emotion Recognition Performance between CHR-Unmedicated and CHR-Medicated.

	Variable	1	2	3	4	5	6	7	8
1.	Left amygdala	__	.33**	.81**	-.13	.76**	-.07	.03	.40**
2.	Right amygdala	.54**	__	.82**	-.12	.74**	-.05	.08	.45**
3.	Total amygdala	.86**	.88**	__	-.15	.90**	-.07	.06	.52**
4.	Prefrontal Cortex	-.16*	-.07	-.09	__	-.56**	-.09	-.29*	.24*
5.	Amygdala:Prefrontal	.84**	.81**	.93**	-.43**	__	-.00	.16	.33**
6.	FER Performance	-.15*	-.07	-.12	-.16*	-.16*	__	.08	-.17
7.	Age	.21**	.10	.17*	-.44**	.32**	-.21**	__	.08
8.	ICV	.40**	.42**	.46**	.21**	.05	.05	-.08	__

Note. Intercorrelations for CHR-Unmedicated (n=167) are presented below the diagonal and intercorrelations for CHR-Medicated (n=71) are presented above the diagonal. FER=Facial Emotion Recognition.
*$p < .05$, **$p < .01$

Table 4

Regression Analyses for Neuroanatomical Predictors of Facial Emotion Recognition Performance by Group

	Group					
	CHR-Unmedicated		CHR-Medicated		Controls	
Predictor	ΔR^2	β	ΔR^2	β	ΔR^2	β
Block 1	.06*		.05		.05	
Control Variables[a]						
Block 2	.01*		.001		.006	.
Amygdala		-.13		.03		-.08
Prefrontal		-.01		-.01		.03
Block 3	.03**		.03		.007	
Amygdala:Prefrontal		.18*		-.18		-.08
Total R^2	.10**		.07		.06	
n	167		71		119	

[a] Control variables included age, sex, and ICV
*$p < .05$, **$p < .01$

Figure 1

Structural magnetic resonance image of human brain highlighting the major components of the amygdala-prefrontal circuitry.

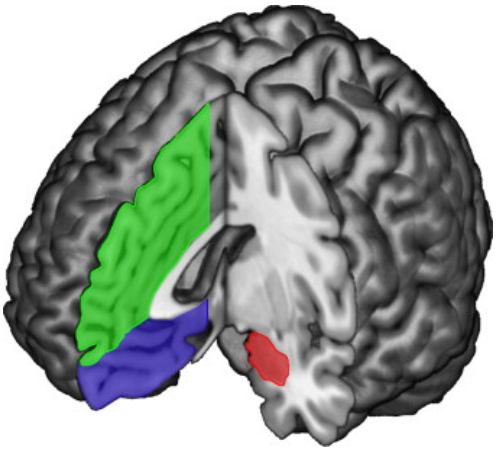

Figure 1. Amygdala (red), ventromedial prefrontal cortex (blue), and dorsomedial prefrontal cortex (green). Adapted from "The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety," by Kim et al., 2011, Behavioral Brain Research, 223(2), p. 404.

Figure 2

Group Mean Differences in Anatomical Regions of Interest and Facial Emotion Recognition Performance in CHR vs. Controls

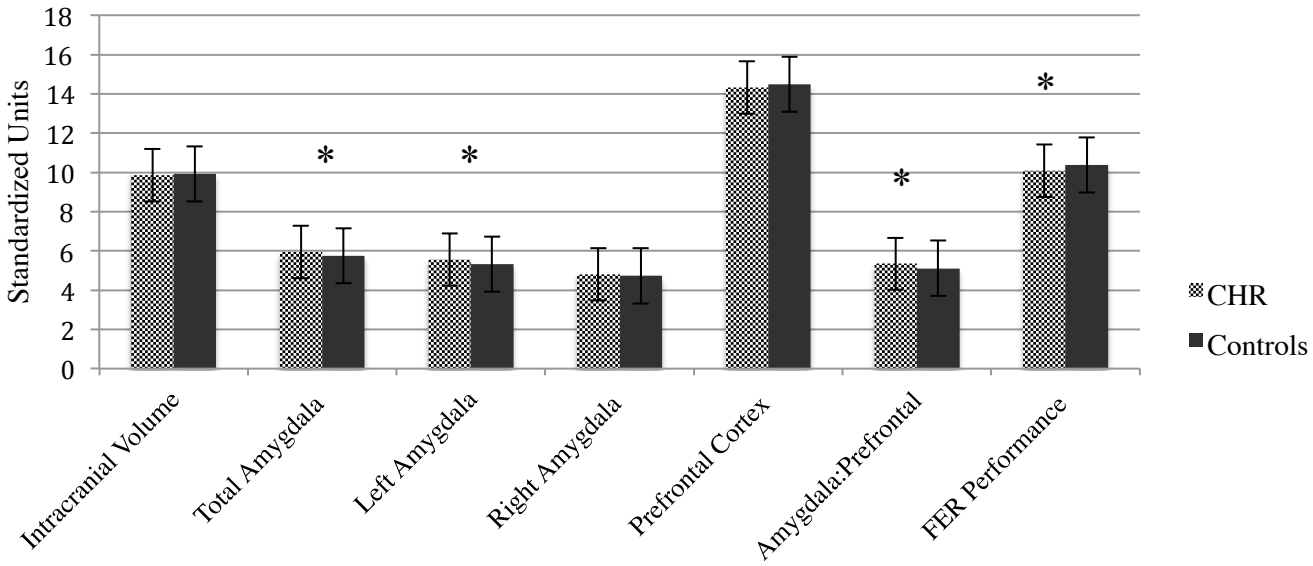

Figure 2. All variables used in these comparisons were standardized. Region of Interest Variables are absolute volumes. FER= Facial Emotion Recognition Performance.

Figure 3

Group Mean Differences in Anatomical Regions of Interest and Facial Emotion Recognition Performance in CHR-Unmedicated vs. CHR-Medicated vs. Controls.

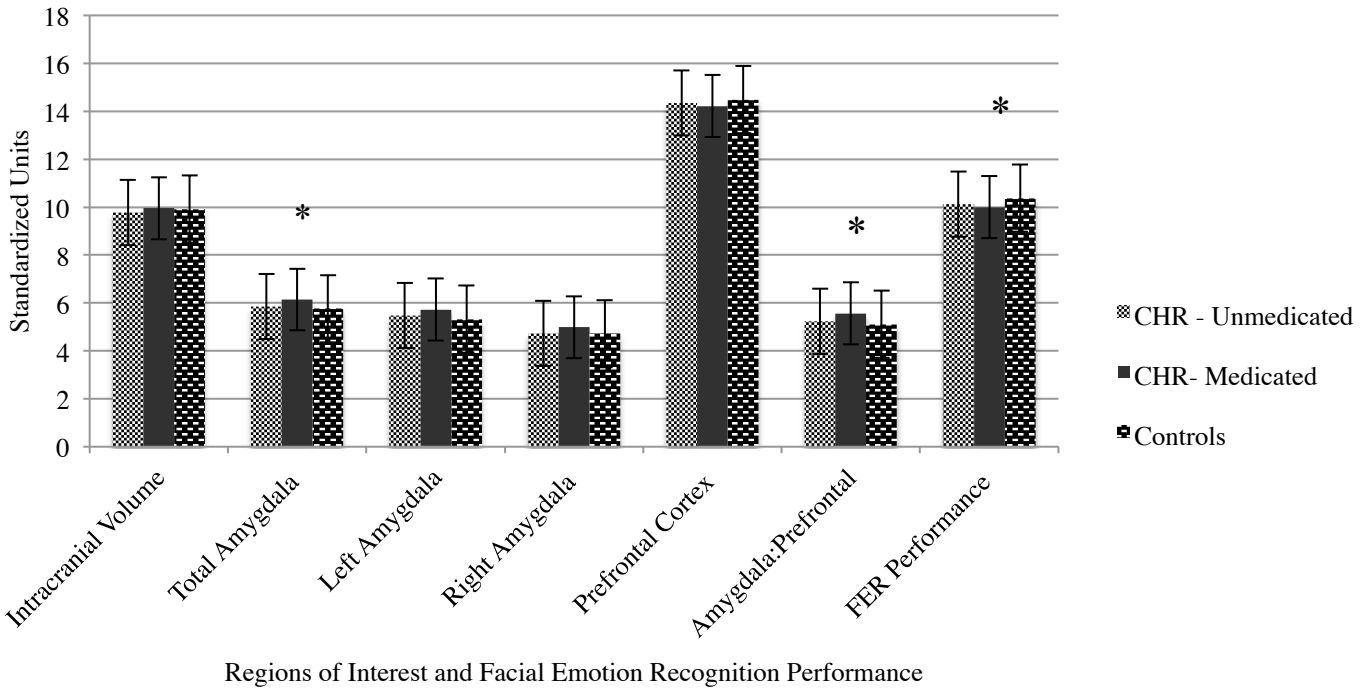

Figure 3. All variables used in these comparisons were standardized. Region of Interest Variables are absolute volumes. FER= Facial Emotion Recognition Performance