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# Relationship between amygdala volume and emotion recognition in adolescents at ultra-high risk for psychosis

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ABSTRACT

Amygdala volume has been proposed as a neural risk biomarker for psychotic illness, but findings in the ultra-high risk for psychosis (UHR) population have been somewhat inconsistent, which may be related to underlying social cognitive abilities. The current study investigated whether amygdala volumes were related to emotion-recognition impairments in UHR individuals, and whether volumes differed by sex. Secondary aims were to assess whether (a) emotion-recognition performance was associated with interhemispheric amygdala volume asymmetry and (b) amgydala volume and volume asymmetry acted as a mediator between emotion-recognition and outcome measures. The amygdala was manually delineated from magnetic resonance images for 39 UHR individuals who had also completed facial and prosody emotion-recognition tasks. Partial correlations were conducted to examine associations between amydgala volume/asymmetry and recognition of negative emotions. Mediation analyses were conducted using regression and bootstrapping techniques. Amygdala volume was positively correlated with sadness emotion recognition, in particular prosody, for females only. Left amygdala volume mediated the effect of sadness recognition on depressive symptoms, negative symptoms, overall psychopathology, and global functioning in females. Findings suggest a complex relationship between emotion recognition, the structure of the amygdala and illness outcome, where recognition of sadness appears to be the precipitator of this relationship in UHR females. Further research is needed to determine illness specificity and to confirm our sex- and emotion-specific results.


## 1. Introduction

The amygdala is essential for emotion recognition (ER; Adolphs, 2001) and is most prominently linked to negatively valenced emotions, namely sadness, anger and fear (Adolphs et al., 1999; Adolphs and Tranel, 2004). Reduced amygdala volumes are generally found to be associated with poorer ER (Adolphs and Tranel, 2004; Nacewicz et al., 2006). There is solid evidence of impaired ER, particularly for negative emotions, in established schizophrenia (Edwards et al., 2002; Hoekert et al., 2007; Chan et al., 2010) and first episode psychosis (FEP; Edwards et al., 2001; Thompson et al., 2012), and there is also emerging evidence in individuals at ultra-high risk (UHR) of psychosis (Thompson et al., 2011; Amminger et al., 2012a; Amminger et al., 2012b; Green et al., 2012; Thompson et al., 2012). Given these findings, researchers have begun to investigate the structure of the amygdala as a possible neural risk biomarker for psychotic illness (e.g., van Winkel et al., 2013).

The UHR approach identifies a unique 'clinical' help-seeking population composed of individuals who are at increased risk of developing psychosis (approximately 17% will transition to a psychotic disorder within an average of 22 months) (Wiltink et al., 2013). The UHR age range is typically 14–30 years, the life period with the highest risk for psychosis onset. Findings of the limited number of studies that have investigated amygdala volumes in UHR patients have been inconclusive, with some studies suggesting amygdala volumes are normal in this population (Velakoulis et al., 2006; Witthaus et al., 2010), and others finding decreases bilaterally (Bechdolf et al., 2012). A number of factors could account for the inconsistent findings, including

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individual differences in ER impairment within samples, which may bias group findings one way or another. However, no study to date has investigated the relationship between amygdala structure and ER ability in UHR individuals. Only one published study has investigated this relationship in schizophrenia, and it found that smaller left amygdala volumes were associated with deficits in facial recognition of sadness (Namiki et al., 2007). If such a relationship were found in UHR individuals, it would provide the first evidence for putative premorbid structural abnormalities that correspond to difficulties in recognising specific emotions, and would support the suggestion that the amygdala has a potential role in the development of psychotic disorders.

Sex differences in ER are well established in the healthy population, with females being consistently more accurate than males in processing and interpreting facial expressions (e.g., McClure, 2000; Williams et al., 2009). A recent meta-analysis concluded that females have increased activation, particularly in the left amygdala, in relation to negative emotion processing in comparison to males (Stevens and Hamann, 2012). This is in line with the previously reported sex-dependent lateralization of amygdala involvement in emotional memory (Cahill et al., 2001). Interestingly, several studies have found female schizophrenia patients to outperform their male counterparts on emotion-recognition tasks (Scholten et al., 2005; Van't Wout et al., 2007; Erol et al., 2013), but the limited ER research in UHR has not yet specifically explored the effects of sex. Given these findings, and evidence of sex-specific amygdala volume abnormalities in first episode psychosis (Frazier et al., 2008) and established schizophrenia (Gur et al., 2004; Niu et al., 2004), the current study will explore associations in each sex, separately. In addition, a reduction in the normal pattern of brain regional asymmetries has been noted in psychotic disorders (e.g. Yucel et al., 2002). Also, amygdala asymmetry has been found to be sex-dependent in patients with first episode psychosis, whereby only females have been shown to have a higher degree of asymmetry compared with healthy controls (Gibbs et al., 2008). Therefore, we will also explore the association between amygdala asymmetry and ER performance for males and females.

The primary aim of the present study was to investigate the possible relationship between recognition of negatively valenced emotions (sadness, anger, fear) and amygdala volumes in male and female UHR individuals. It was hypothesised that smaller amygdala volumes would be associated with larger ER deficits for both facial and prosodic emotion, and that this would be more pronounced in females. Secondary aims were to (a) examine whether ER was associated with interhemispheric amygdalae volume asymmetry and (b) explore the relationship between amygdala volume and symptomatology/functioning, and, where significant correlations are found, the potential mediating role of amygdala volume between ER and these illness dimensions.

## 2. Methods

### 2.1. Participants

UHR participants were recruited from the Department of Child and Adolescent Psychiatry, Medical University of Vienna, Austria, for a larger randomised controlled study, described previously (Amminger et al., 2010). Of the 81 participants recruited for this larger study, a subsample of 43 underwent magnetic resonance imaging (MRI) and behavioural assessment as part of the current study's protocol. Of these participants, three were excluded from analyses due to movement artefacts/poor image quality, and one person was excluded for failure to complete the ER task, leaving a final total sample of 39 UHR individuals.

All individuals were eligible for participation if they were aged 13–25 years and met criteria for one or more of the following three operationally defined and well-validated UHR subgroups: attenuated positive psychotic symptoms, transient psychosis, and family history of psychosis plus a decrease in functioning. To determine whether participants fell into one of these subgroups, a semi-structured interview involving the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to specifically assess the presence of attenuated psychotic symptoms and transient psychosis. Cut-off scores for symptom severity were those proposed by Morrison et al. (2004). Frequency and duration criteria used in the current study were according to Yung et al. (1998). Family history of a psychotic disorder in a first-degree relative was assessed with the Family History Research Diagnostic Criteria (Endicott et al., 1978). All UHR individuals were free of antipsychotic medication. Ethics approval was granted by the Ethics Committee of the Medical University of Vienna, Austria. All participants provided written informed consent, including parental consent for those less than 18 years of age.

### 2.2. Assessment of emotion recognition

Facial ER was assessed with the Facial Emotion-Labelling Task, a computerised modification of the Feinberg et al. (1986) task. Stimuli, consisting of 21 slides from Ekman and Friesen (1976), were black and white photographs of faces representing standardized poses of fundamental emotions including sadness, anger, happiness, disgust, surprise, fear, and neutral (3 photographs per emotion). For the purpose of the current study, however, we focused our analyses on sadness, anger, and fear, given that the amygdala is more robustly associated with the processing of these negatively valenced expressions, and in order to reduce the likelihood of Type I error. Participants labelled the emotion expressed by the face from multiple choice options. Exposure time to photographs was 0.5 s, with a 1-s interstimulus interval. This task has previously been validated in a sample of young people with first episode psychosis (Edwards et al., 2001).

Prosody was assessed with the affective prosody task developed by Edwards and colleagues (Edwards et al., 2001). Three professional actors spoke 16 simple sentences, which comprised variations of the four sentences used by Roberts et al. (1981): “They must stay here”, “He will come soon”, “She will drive fast” and “We must go there”. The sentences were spoken by the actors in five different moods, including fear, sadness and anger. There were 60 items in the final task with 8 s of silence in between each item. Participants were given multiple choice emotion categories for each item, with responses recorded as incorrect=0 and correct=1. Item-retention rules were based on percentage-correct results of university students (Edwards et al., 2001). This task has been previously validated in a sample of adolescents/young adults with first episode psychosis (Edwards et al., 2001).

### 2.3. Measures of psychopathology, depression and general functioning

The PANSS (Kay et al., 1987) was administered to assess symptom severity, in addition to determining UHR status. The PANSS subscales (Positive, Negative and General psychopathology) and the total score (referred to as Overall psychopathology) were used as outcome variables.

The Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) was used to assess the frequency and severity of depressive symptoms. It consists of 10 items assessing apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude (inability to get going), inability to feel, pessimistic thoughts and suicidal thoughts. The maximum score is 60. It has excellent validity and reliability, as measured against other depression rating scales (Montgomery and Åsberg, 1979).

To assess overall functioning, including psychosocial and occupational, we used the Global Assessment of Functioning scale (GAF) (Jones et al., 1995). It is recorded as a single score ranging from 0 (severely impaired functioning) to 100 (superior functioning). The GAF has been shown to be a reliable and valid measure of psychiatric disturbance (Jones et al., 1995).

Current estimated IQ of participants was measured with the Zahlen–Verbindungs-Test (ZVT; the number combination test) (Oswald and Roth, 1987). The ZVT is a trail-making test in which subjects draw lines to connect, in order, circled numbers from 1 to 90 which are positioned more or less randomly on a piece of paper. It represents a highly reliable measure of information-processing speed that correlates highly with standard psychometric tests of intelligence (Rammsayer and Stahl, 2007).

### 2.4. Image acquisition and pre-processing

Participants underwent MRI at DiagnoseZentrum Urania diagnostic centre in Vienna. A 1.5 Tesla Philips Intera scanner generated 90 contiguous, 1.5-mm coronal sections. Imaging parameters were as follows: echo time, 9.2 ms; repetition time, 30 ms; flip angle, 30°; matrix size, 256 × 256; field of view: FH 22 cm, RL 19.7 cm, AP 17.2 cm; and voxel dimensions, 1.15 × 1.15 × 1.5 $mm^3$.

Pre-processing involved linear registration of images to the Montreal Neurological Institute (MNI) 152 average template (six-parameter rigid body transformations with trilinear interpolation) using FLIRT (Jenkinson and Smith, 2000). This registration served to align each image axially along the anterior commissure-posterior commissure plane and sagittally along the interhemispheric fissure, without any deformation. Images were re-sliced into 1-mm isotropic voxels.