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Regional grey matter volume and concentration in at-risk adolescents: Untangling associations with callous-unemotional traits and conduct disorder symptoms

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ABSTRACT

Structural Magnetic Resonance Imaging studies have reported volume reductions in several brain regions implicated in social cognition and emotion recognition in juvenile antisocial populations. However, it is unclear whether these structural abnormalities are specifically related to antisocial features, or to co-occurring callous-unemotional (CU) traits. The present study employed voxel-based morphometry to assess both grey matter volume (GMV) and grey matter concentration (GMC) in a large representative at-risk sample of adolescents (n=134; mean age 17.7 yr), characterized by a broad range of CU trait and conduct disorder (CD) symptom scores. There was a significant interaction between CD symptom and CU trait scores in the prediction of GMV in the anterior insula, with a significant positive association between CU traits and GMV in youth low on CD symptoms only. In addition, we found a significant unique positive association between CD symptoms and GMC in the amygdala, and unique negative associations between CU traits and GMC in the amygdala and insula. These findings are in line with accumulating evidence of distinct associations of CD symptoms and CU traits with amygdala and insula GMC in juvenile antisocial populations.

1. Introduction

Children who exhibit antisocial behaviour are at risk of persistent criminality, as well as a wide range of physical and mental health problems (Odgers et al., 2007). However, they are not all the same. For example, some children with antisocial behaviour also have high levels of callous-unemotional traits (CU traits; i.e. they lack empathy and remorse) and this differentiates them from other antisocial children with respect to several important etiological, clinical and criminological factors: children with these traits have severe and persistent conduct problems, display resistance to some conduct problem interventions, seem to be characterized by distinct neurobiological correlates and appear more genetically vulnerable to antisocial behaviour (Frick et al., 2014; Viding et al., 2012). The importance of this distinction is also reflected in the fact that the latest edition of the Diagnostic Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) includes CU traits as a specifier for conduct disorder: 'low prosocial emotions'.

While much remains unknown about the pathogenesis of antisocial behaviour and CU traits, it is increasingly clear that children and juveniles showing these traits are characterized by severe disturbances in emotion processing (see Blair (2013) for a thorough review). An increasing number of functional MRI studies have reported atypical brain function in several core emotion processing regions in antisocial youths, when compared to typically developing children, including in the amygdala (Marsh et al., 2008; Jones et al., 2009; Viding et al., 2012; White et al., 2012), insula (Rubia et al., 2009; Lockwood et al., 2013; Sebastian et al., 2012) and orbitofrontal cortex (OFC; Finger et al., 2011, 2008; Rubia et al., 2009). Structural brain differences are also seen in these areas, with a number of studies in children and adolescents with conduct disorder (CD) as well as adults with antisocial personality disorder (ASPD), reporting decreased grey matter volume

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(GMV) compared to healthy controls in the amygdala (Huebner et al., 2008; Wallace et al., 2014; Sterzer et al., 2007; Fairchild et al., 2011; Yang et al., 2009), insula (de Oliveira-Souza et al., 2008; Tiihonen et al., 2008; Sterzer et al., 2007; Fairchild, 2011; Fairchild et al., 2013), and OFC (Yang et al., 2010; Tiihonen et al., 2008; Huebner et al., 2008; Sebastian et al., 2015; although see De Brito et al., 2009; Michalska et al., 2015 for opposite or null findings). Two recent meta-analyses confirm insula GMV reductions in antisocial individuals of all ages (Aoki et al., 2013), and insula (extending into ventrolateral prefrontal cortex) and amygdala GMV reductions in antisocial children and adolescents (Rogers and De Brito, 2015). Many studies have assessed the unique associations between GMV and either CU traits or antisocial behaviour (i.e. variance of one dimension not shared with the other dimension), in recognition of the partially distinct etiology of these dimensions (Viding and McCrory, 2012). Fairchild et al. (2011) reported a unique negative association between CD symptoms and insula GMV. With regard to GMV in the OFC, there have been reports of both positive (Fairchild et al., 2013) and negative (Ermer et al., 2013; Sebastian et al., 2015) unique associations with CU traits and positive (Ermer et al., 2013) and negative (Ermer et al., 2012) unique associations with antisocial behaviour. The dimensional analyses have yielded consistent null results in the amygdala for both CD symptoms and CU traits (Fairchild et al., 2013, 2011; Ermer et al., 2012, 2013; Sebastian et al., 2015).[1]

Although these initial findings are exciting, the heterogeneity of the samples that have been studied (in terms of measures used to chart CD and CU symptoms, age and sex of participants, sample size and the range of behavioural scores represented), as well as the dearth of replication analyses, mean that we do not yet have a clear picture of the respective contributions of CD and CU symptoms on brain structure. Furthermore, most of these studies only report associations with GMV, and not Grey Matter Concentration (GMC). GMV and GMC measures tend to be correlated, but they are thought to reflect different aspects of brain structure (Good et al., 2001; Mechelli et al., 2005): absolute regional volume (GMV) versus regional grey matter density (GMC). While GMV has been the mainstay of VBM research, recent evidence suggests that GMC may be more sensitive and specific at detecting volumetric differences than GMV (Radua et al., 2014). Indeed, one study reported differential association patterns of antisocial behaviour and CU traits with GMV and GMC, respectively (Ermer et al., 2012).

The current study used VBM to investigate the unique associations of CD and CU symptoms with GMC, as well as GMV, in a large sample of well-characterized at-risk youths with a broad symptom severity range. All participants had at least one recorded offence that took place before age 12. Based on findings from previous functional and structural MRI studies comparing groups of antisocial individuals with healthy controls, we selected the amygdala, insula, and OFC as *a priori* regions of interest (ROIs), and hypothesized that variance uniquely attributable to CU traits and CD symptoms would be negatively and positively associated, respectively, with amygdala GMC and GMV – given previous reports of such association patterns with function in this region (Sebastian et al., 2012; Lozier et al., 2014), while investigation of their relation with structure in the insula and OFC was more explorative.

[1] Walters and Kiehl (2015) do report a negative association between amygdala GMV and a 'fearlessness' measure derived from items from Factors 1 and 2 of the Psychopathy Checklist: Youth Version, controlling for a 'disinhibition' measure derived from Factor 3.

2. Methods

2.1. Participants

Participants were recruited from a Dutch national cohort of 364 adolescents who were all childhood arrestees with an index crime before age 12, including petty theft, arson, vandalism, trespassing, burglary, assault, sexual abuse and robbery. They had already participated in three previous waves of this longitudinal study (Domburgh et al., 2009): mean age at study entrance was 10.9 (SD 1.4) years and mean age at wave three was 13.1 (SD 1.5) years. For the current neuroimaging study (wave four; mean age 17.7 (SD 1.6) years), a subsample (total n=150) was recruited, ensuring participants to cover the complete severity spectrum of antisocial behaviour and psychopathic traits (see Table 1). This was accomplished by recruiting participants with a low risk, a medium risk and a high risk for antisocial behaviour and psychopathic traits. Low risk participants were those without a DSM-IV Disruptive Behaviour Disorder [DBD; Oppositional Defiant Disorder, ODD, or CD] diagnosis in the three previous waves according to the Diagnostic Interview Schedule for Children version IV [DISC-IV], and with aggression scores [Reactive Proactive Aggression Questionnaire; RPQ] and CU trait scores [Youth Psychopathic Traits Inventory; YPI, CU subscale] below the median during all previous waves (n=37 out of the original n=110). Medium-risk participants were those with above-median scores on aggression [RPQ] and CU traits [YPI] during previous waves, but no previous DSM-IV diagnosis of DBD (n=57 out of the original n=174). High-risk participants were those with a DSM-IV DBD diagnosis on at least one of the previous waves (n=56 out of the original n=80). A total of 16 participants were excluded from the analyses because of missing data (n=1), intracerebral cysts (n=6) or missing MRI data due to artifacts (n=9). All analyses were performed continuously across the entire final sample (n=134).

2.2. Procedure and image acquisition

The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2008, and was approved by the IRB of the VU University Medical Center Amsterdam (VUmc). All participants (and their parents/custodians, if age of the participant was below 18) signed informed consent and were visited at home for a structured psychiatric interview (Diagnostic Interview Schedule for Children version IV; DISC-IV) and self-report questionnaires, including the Youth Psychopathic Traits Inventory

Table 1
Socio-demographic and mental health characteristics of the current sample (n=134).

CD symptoms, mean (SD), range	1.0 (1.9), 0–9
YPI Callous-Unemotional, mean (SD), range	24.3 (7.1), 15–55
ODD no.(%)	16 (11.9%)
CD no. (%)	18 (13.4%)
Age, mean (SD), range	17.7 (1.5), 12–20
Male gender, no. (%)	114 (85%)
Low SES neighborhood, no. (%)	73 (54.4%)
Non-Western ethnicity, no. (%)	36 (27%)
IQ, mean (SD), range	91.3 (13.5), 62–126
CBCL Internalizing, mean T-score (SD), range	51.1 (10.8), 33–77
YSR Internalizing, mean T-score (SD), range	47.6 (10.0), 30–75
CBCL Externalizing, mean T-score (SD), range	51.8 (11.4), 34–78
YSR Externalizing, mean T-score (SD), range	52.4 (10.1), 34–77
ADHD no. (%)	40 (29.9%)
PTSD no. (%)	2 (1.5%)

Abbreviations: CD: Conduct Disorder, YPI: Youth psychopathic traits inventory, SES: Socio-economic status, CBCL: Child Behaviour Checklist, YSR: Youth Self Report, ADHD: Attention Deficit/Hyperactivity Disorder, ODD: Oppositional Defiant Disorder, PTSD: Post-Traumatic Stress Disorder.