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Cognitive reappraisal of peer rejection in depressed versus non-depressed adolescents: Functional connectivity differences

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ABSTRACT

Background: Depression is the most common psychiatric disorder in adolescence, and is characterised by an inability to down-regulate negative emotional responses to stress. Adult studies suggest this may be associated with reduced functional connectivity between prefrontal and subcortical regions, yet the neurological mechanisms in adolescence remain unclear.
Methods: We developed a novel, age-appropriate, reappraisal paradigm to investigate functional connectivity during reappraisal of a real-life source of stress in 15 depressed and 15 non-depressed adolescents. During fMRI, participants i) attended to, and ii) implemented reappraisal techniques (learnt prior to fMRI) in response to, rejection.
Results: Reappraisal reduced negative mood and belief in negative thoughts in both groups alike, however during reappraisal (versus attend) trials, depressed adolescents showed greater connectivity between the right frontal pole and numerous subcortical and cortical regions than non-depressed adolescents.
Conclusions: These findings tentatively suggest that, when instructed, depressed adolescents *do* have the ability to engage neural networks involved in emotion regulation, possibly because adolescence reflects a period of heightened plasticity. These data support the value of cognitive reappraisal as a treatment tool, identify neural markers that could be used to optimise current therapies, and lay the foundations for developing novel neuroscientific techniques for the treatment of adolescent depression.

Major depressive disorder (MDD) is one of the most common adolescent mental health problems (World Health Organisation, 1992) and can persist into adulthood where it is extremely debilitating and costly (Weissman et al., 1999). Efforts to understand the mechanisms by which adolescent depression arises and abates are therefore a major research priority. Psychosocial stress in general, and peer rejection specifically, are strongly associated with adolescent depression (Thapar et al., 2012). However, as interpersonal stressors are common during adolescence, and as not all young people develop depressive disorders in response to these, diathesis-stress models implicate latent factors that might explain why depressed adolescents are more vulnerable to peer rejection than others (Braet et al., 2012). In this study we investigate i) whether adolescent depression is characterised by an inability to deploy an effective emotion regulation strategy during peer rejection, and ii) whether atypical functional connectivity between the prefrontal cortex (PFC) and subcortical regions may underlie this difficulty.

A growing body of research shows evidence of poor emotion regulation (ER) – the process of modifying the magnitude, valence or duration of an emotional response (Gross, 2002) – in depressed

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adolescents. Adolescents with depressive symptoms report greater use of maladaptive ER strategies (e.g. self-blame, rumination, catastrophizing) and less use of adaptive cognitive strategies (e.g. reappraisal; re-interpreting a negative situation as benign), than peers with fewer symptoms (Garber et al., 1995; Garnefski and Kraaij, 2006). However, these data do not speak to the ability of depressed adolescents to employ more adaptive strategies when instructed. The biological mechanisms underlying ER difficulties may be elucidated using functional magnetic resonance imaging (fMRI).

Several pioneering experiments have reported neural differences in cognitive reappraisal between depressed and non-depressed adults (Ochsner et al., 2012). Typically in these studies, participants are given reappraisal training prior to fMRI, in which they learn to decrease negative responses by re-framing a negative event/photo (e.g. it is not as bad as it looks) (Ochsner et al., 2004). During fMRI, participants' responses during the implementation of training (instructed cognitive reappraisal) are compared with when they simply observe the negative stimuli (uninstructed ER). Although behavioural data suggest depressed adults are as able to use instructed cognitive reappraisal as non-depressed adults, they show distinct patterns of brain activity (Erk et al., 2010; Heller et al., 2009; Johnstone et al., 2007). A review of studies of *psychiatrically-healthy* adults identified three major regions engaged during cognitive reappraisal: 1) dorsolateral prefrontal cortex (DLPFC), posterior PFC and inferior parietal lobe (IPL; involved in selective attention and working memory), 2) dorsal anterior cingulate cortex (dACC; thought to be involved in tracking the success of reappraisal), and 3) ventrolateral PFC (VLPFC; which may play a role in selecting goal-appropriate responses from semantic memory) (Ochsner et al., 2012). These mostly prefrontal regions are suggested to regulate emotion by directly modifying responses in sub-cortical regions (e.g. the amygdala, ventral striatum and insula) associated with emotional reactivity (McRae et al., 2008; Ochsner et al., 2004; Phan et al., 2005). Depressed individuals deviate from this pattern by showing heightened activity in affective areas (e.g. amygdala, insula, dACC), reduced activity in prefrontal areas (e.g. DLPFC), reduced connectivity between these regions and difficulties sustaining ER-related neural changes over time (Erk et al., 2010; Heller et al., 2009).

Outstanding questions remain about whether these differences are also associated with adolescent depression. Although PFC regions associated with cognitive reappraisal undergo protracted maturation during adolescence (Cohen Kadosh et al., 2013), data from typically-developing youths reveal a remarkably similar network of regions involved in ER to that in adults (Levesque et al., 2004; McRae et al., 2012; Pitskel et al., 2011). In line with studies of *uninstructed* ER in depressed adults (Dannlowski et al., 2007; Tang et al., 2007; Victor et al., 2010) and adolescents (Davey et al., 2011; Masten et al., 2011), one recent study found depressed adolescents showed greater activity than controls in the right amygdala in the maintain (versus reappraisal) condition (Perlman et al., 2012). Also replicating adult studies (Kong et al., 2013), this study showed there was *less* connectivity between the amygdala and the insula and medial PFC during this condition, suggesting adolescent depression may be associated with impaired neural control over affective responses. In contrast to adult studies (Erk et al., 2010; Goldin et al., 2009), however, during instructed reappraisal patients showed *greater* connectivity between the amygdala and the left medial frontal gyrus (MFG) and subgenual anterior cingulate cortex than controls (Perlman et al., 2012). Tentatively, these findings suggest that during instructed reappraisal, depressed adolescents seem more able to address their pre-existing ER-difficulties than healthy participants. It may be that instructed cognitive reappraisal training has greater effects in the depressed group because their symptom severity affords greater potential for change. It is possible that this advantage is seen in adolescents, but not adults, because prefrontal regions undergo continuous experience-dependent pruning during adolescence and are therefore relatively plastic (Cohen Kadosh et al., 2013).

While these preliminary data involving reappraisal of static emotional photos are intriguing, it is unclear whether these neural differences apply when adolescents are asked to reappraise real-life interpersonal stressors. In this study, we therefore experimentally delivered a real-life source of stress – peer rejection. A number of experimental tasks have been used to simulated peer rejection and measure associated behavioural and neural processes, including Cyberball (Williams et al., 2000), the Social Judgement Task (Somerville et al., 2006), the Yale Interpersonal Stressor (Stroud et al., 2000) and Chatroom (Guyer et al., 2009) (see (Platt et al., 2013) for a review). Using these paradigms, in which adolescents are instructed to deploy 'natural' processes of ER, heightened neural activity in the subgenual anterior cingulate cortex appears to characterise depressed versus non-depressed adolescents (Silk et al., 2014) and predicts depressive symptoms at one year follow-up amongst typically developing adolescents (Masten et al., 2011). Nevertheless, these paradigms have not yet been used to assess behavioural and neural processes associated with instructed ER in adolescents. Adapting reappraisal training paradigms to target age-appropriate stressors during adolescence is also a vital next step if neuroscientific data are to inform treatment models. We therefore developed a novel reappraisal technique which trained adolescents' re-interpretation of various age-appropriate social scenarios, and which they were then asked to apply when they received negative feedback from peers in the Chatroom task. We contrasted functional connectivity between instructed (cognitive reappraisal) and uninstructed (attend) ER conditions in depressed and non-depressed adolescents. Our main analysis explored depression-associated differences in functional connectivity during instructed (versus uninstructed) ER. In line with the results of a previous adolescent study (Perlman et al., 2012), we hypothesised that depressed (versus non-depressed) adolescents would show increased connectivity between the prefrontal cortex and sub-cortical regions during reappraisal versus attend trials. We used whole-brain analysis to identify which brain regions were associated with reappraisal, rather than selecting *a priori* regions of interest (ROI) for the connectivity analysis. Although there is a relatively established literature on the neural networks involved in instructed ER in adults, the adolescent literature remains less well developed.

1. Material and methods

1.1. Sample and recruitment

Fifteen medication-free adolescents (aged 15–17) with a current diagnosis of MDD according to DSM-IV were recruited from local Child and Adolescent Mental Health Services (CAMHS) and schools. Fifteen non-depressed adolescents with no current or previous psychiatric history were recruited from local schools. Participants were excluded if they had a low IQ (Wechsler Intelligence Scale for Children (III) score < 70) (Wechsler, 1991) or MRI incompatibility. Depressed adolescents were excluded if they had another psychiatric diagnosis (other than anxiety) or if they reported current suicidal intent or a recent suicide attempt, due to concerns that the rejection manipulation may exacerbate suicidal behaviour.

Participant demographics are described in Table 1. There were no significant differences between the groups in demographic variables ($Ps > 0.05$). Although there were only two males in each group, this may reflect the actual gender ratio in depression