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Research report

Aberrant brain responses to emotionally valent words is normalised after cognitive behavioural therapy in female depressed adolescents

Jie-Yu Chuang [a,*], Kirstie J Whitaker [a], Graham K Murray [a,b,c], Rebecca Elliott [d], Cindy C Hagan [a,e], Julia ME Graham [a], Cinly Ooi [a], Roger Tait [b], Rosemary J Holt [a], Adrienne O van Nieuwenhuizen [f], Shirley Reynolds [g], Paul O Wilkinson [a], Edward T Bullmore [a], Belinda R Lennox [h], Barbara J Sahakian [a,b], Ian Goodyer [a], John Suckling [a,b,c]

[a] Department of Psychiatry, University of Cambridge
[b] Behavioural and Clinical Neuroscience Institute, University of Cambridge
[c] Cambridgeshire and Peterborough NHS Foundation Trust
[d] Institute of Brain, Behaviour and Mental Health, University of Manchester
[e] Department of Psychology, Columbia University
[f] University of Cambridge
[g] School of psychology and Clinical language Sciences, University of Reading
[h] Department of Psychiatry, University of Oxford

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ABSTRACT

Background: Depression in adolescence is debilitating with high recurrence in adulthood, yet its pathophysiological mechanism remains enigmatic. To examine the interaction between emotion, cognition and treatment, functional brain responses to sad and happy distractors in an affective go/no-go task were explored before and after Cognitive Behavioural Therapy (CBT) in depressed female adolescents, and healthy participants.

Methods: Eighty-two Depressed and 24 healthy female adolescents, aged 12–17 years, performed a functional magnetic resonance imaging (fMRI) affective go/no-go task at baseline. Participants were instructed to withhold their responses upon seeing happy or sad words. Among these participants, 13 patients had CBT over approximately 30 weeks. These participants and 20 matched controls then repeated the task.

Results: At baseline, increased activation in response to happy relative to neutral distractors was observed in the orbitofrontal cortex in depressed patients which was normalised after CBT. No significant group differences were found behaviourally or in brain activation in response to sad distractors. Improvements in symptoms (mean: 9.31, 95% CI: 5.35–13.27) were related at trend-level to activation changes in orbitofrontal cortex.

Limitations: In the follow-up section, a limited number of post-CBT patients were recruited.

Conclusions: To our knowledge, this is the first fMRI study addressing the effect of CBT in adolescent depression. Although a bias toward negative information is widely accepted as a hallmark of depression, aberrant brain hyperactivity to positive distractors was found and normalised after CBT. Research, assessment and treatment focused on positive stimuli could be a future consideration. Moreover, a pathophysiological mechanism distinct from adult depression may be suggested and awaits further exploration.

1. Introduction

Adolescence is turbulent with an imbalance in brain maturation between subcortical and prefrontal areas (Casey and Caudle, 2013). Major depressive disorder (MDD) during adolescence is associated with severe functional impairment, suicide, and high recurrence rate in adulthood (Thapar et al., 2012). The pathophysiology of adolescent depression may be elucidated by investigation of the neural correlates. However, in contrast with adult depression, only a few neuroimaging studies have been conducted to date, and no meta-analyses providing a convergent description in adolescents are currently available (Hagan et al., 2013).

* Correspondence to: Herchel Smith Building for Brain and Mind Sciences, Robinson Way, Cambridge CB2 0SZ, United Kingdom. Fax: +44 1223 336581.
E-mail address: jc756@cam.ac.uk (J.-Y. Chuang).

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In everyday life, most adults are able to suppress responses to neutral or emotional distractions to achieve goals. By contrast, adolescence is associated with heightened reactivity and poor self control when facing positive or negative emotional cues (Casey, 2014). This may be enhanced in depressed adolescents who respond more impulsively when faced with an emotionally valent distractor in a inhibitory control task (Maalouf et al., 2012). In fact, even with neutral stimuli, aberrant response to distractors has been associated with suicidality in adolescent depression (Pan et al., 2011). Indeed, attentional bias towards emotional stimuli has been postulated to be a significant component in the aetiology and maintenance of depression (Epp et al., 2012) with a resulting disturbance to daily performance.

A common task exploring attentional bias, the affective go/no-go (AGNG) task requires participants to respond (e.g. press a button) to target ('go') stimuli that are emotionally valent (e.g. sad) whilst inhibiting their response to distractor ('no-go') stimuli of different valence (e.g. happy). From a functional imaging perspective, activation is increased in healthy adults in lateral inferior prefrontal cortex in response to positive versus neutral distractors, and in anterior cingulate, insula and hippocampus in response to negative versus neutral distractors (Van Holst et al., 2012). Compared with healthy adults, depressed adults show increased activation in the right lateral orbitofrontal cortex and bilateral anterior temporal cortex in response to sad versus neutral distractors (Elliott et al., 2002) which seemingly indicates a bias toward negative information. However, the ability of positive stimuli to induce aberrant activations has also been demonstrated in a depression meta-analysis (Groenewold et al., 2013). Indeed, despite a general belief that mood-congruent stimuli should be more salient in depression (Epp et al., 2012), the supporting evidence from affective neuroscience is not conclusive. First, a fMRI meta-analysis of emotional tasks in adults with depression has demonstrated that both positive and negative stimuli induce extended and overlapping abnormal activations (Groenewold et al., 2013). More specific to attentional bias, a further meta-analysis reveals the ability of positive stimuli to exert large stroop-like effects on depressed patients (Epp et al., 2012). Furthermore, a review of the literature indicates that numerous studies failed to demonstrate attentional bias towards negative information in depression (Elliott et al., 2011). Rather, there is the suggestion of a general, rather than emotion-congruent attentional bias, or argument for biases in more effortful processing such as interpretation and memory instead of attention (Epp et al., 2012). However, there is also a debate on the general difficulty in conflict monitoring or inhibition (Epp et al., 2012). It has even been suggested that a shared reaction to threat is perceived regardless of valence in these tasks (Epp et al., 2012). Different tasks and heterogeneity in patients may also contribute to the inconsistent findings (Elliott et al., 2011). Consequently, we investigated the responses to both sad versus neutral and happy versus neutral distractors in adolescent depression.

UK National Institute for Health and Care Excellence guidelines for the initial clinical management of moderate to severe MDD in adolescence recommends that a psychological therapy be offered or combined with a selective serotonin uptake inhibitor (SSRI, specifically fluoxetine) (Hopkins et al., 2015). CBT is arguably the most commonly used psychotherapy with several neuroimaging studies conducted in adults. In addition to mutual modulation of several cortico-limbic regions, CBT is associated with changes in prefrontal regions more than subcortical structures, which are likely to be regulated by antidepressants (Kennedy et al., 2007). CBT treatment effects in adult depression have been demonstrated in ventromedial prefrontal cortex (Ritchey et al., 2011), medial prefrontal cortex (Kennedy et al., 2007; Yoshimura et al., 2013), occipital-temporal cortex (Kennedy et al., 2007), orbitofrontal cortex (Kennedy et al., 2007), ventral (Yoshimura et al., 2013) and dorsal anterior cingulate (Kennedy et al., 2007). Aberrancy in response to emotional stimuli has been shown to be diminished in the medial prefrontal cortex (Ritchey et al., 2011; Yoshimura et al., 2013) after CBT. However, despite many similarities, there are prominent differences in treatment responses between adult and adolescent depressed patients; for instance, tricyclic antidepressants are effective only in the former, and SSRI antidepressants are more likely to induce suicidal thoughts in the latter (Thapar et al., 2012). Indeed, the neurophysiological mechanism of CBT in adolescent depression awaits exploration.

We hypothesise that aberrant responses towards happy and sad distractors in the fMRI AGNG task would be observed at baseline and later corrected after CBT in depressed female adolescents. To our knowledge, no previous study has examined brain activation both pre- and post-CBT in depressed adolescents, thus no specific brain region was predetermined as differing between patients and controls. Additionally, gender difference is a long-debated heterogeneity issue with depressed males showing higher ratings of anhedonia (Bennett et al., 2005) and lower tendency to ruminate (Johnson and Whisman, 2013). Consequently, we restricted our analysis to females.

2. Methods

2.1. Participants

Patients were recruited from the Improving Mood with Psychoanalytic and Cognitive Therapies (IMPACT), a pragmatic, effectiveness randomised clinical trial (Goodyer et al., 2011) in East Anglia, North London and North West of England, which is designed to determine the efficacy of psychotherapy. A sub-sample of patients from East Anglia and North London were invited to participate in an adjunctive study, MR-IMPACT, aimed at exploring the pathophysiology of depression using MRI(Hagan et al., 2013). Healthy female controls matched for age, intelligence quotient and handedness were also recruited in the MR-IMPACT study(Hagan et al., 2013).

The data in this analysis were obtained from a longitudinal assessment of patients and controls recruited into MR-IMPACT. All participants underwent baseline assessment. Those IMPACT participants randomized to CBT therapy (Supplementary material 1) and completed multiple CBT sessions (12.85 ± 4.49, range: 5–21 sessions within 243.15 ± 49.81 days) underwent follow-up assessment (Hagan et al., 2013). Control participants were also invited to return for a follow-up assessment. 94 patients and 29 controls were initially recruited with 12 patients and 5 controls excluded due to ineligibility (Supplementary material 2). The exclusion rates between patient and control groups were similar (12/94 and 5/29). Baseline data presented are from 82 depressed and 24 healthy female adolescents (Supplementary material 2) (Table 1): termed the *full group*. Among them, 13 patients and 20 controls returned for follow-up assessment (Table 2), and are termed the *follow-up group*. Demographic data and behavioural measures were compared between the *follow-up group* and the *full group*; the *follow-up group* and those who were not followed up in the *full group* (*full group* minus *follow-up group*).

2.2. Affective go/no-go task (AGNG)

Happy, sad and neutral words were presented to participants during MRI data acquisition using a block paradigm task design (Elliott et al., 2002). Words did not differ in terms of length or usage frequency Hofland K (1982). There were 7 types of blocks each repeating 3 times, consisting of randomly ordered targets/distractors (10 of each type): sad/neutral (SN), sad/happy (SH),