



Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

Cognitive Behavioral Therapy Lowers Elevated Functional Connectivity in Depressed Adolescents

Shayanti Chattopadhyay^{a,*}, Roger Tait^c, Tiago Simas^a, Adrienne van Nieuwenhuizen^a, Cindy C. Hagan^{a,d}, Rosemary J. Holt^a, Julia Graham^{a,e}, Barbara J. Sahakian^{a,c}, Paul O. Wilkinson^{a,b}, Ian M. Goodyer^{a,b,c}, John Suckling^{a,b,c}

^a Department of Psychiatry, University of Cambridge, Cambridge, UK

^b Cambridge and Peterborough Foundation NHS Trust, Cambridge, UK

^c MRC/Wellcome Trust Behavioral and Clinical Neurosciences Institute, University of Cambridge, Cambridge, UK

^d Department of Psychology, Columbia University, New York, NY, USA

^e Department of Psychiatry, University of Oxford, Oxford, UK

ARTICLE INFO

Article history:

Received 13 January 2017

Received in revised form 10 February 2017

Accepted 13 February 2017

Available online xxxx

Keywords:

Depression

Adolescence

Resting-state

Functional connectivity

Fronto-limbic

Cortical thickness

ABSTRACT

Imaging studies have implicated altered functional connectivity in adults with major depressive disorder (MDD). Whether similar dysfunction is present in adolescent patients is unclear. The degree of resting-state functional connectivity (rsFC) may reflect abnormalities within emotional ('hot') and cognitive control ('cold') neural systems. Here, we investigate rsFC of these systems in adolescent patients and changes following cognitive behavioral therapy (CBT). Functional Magnetic Resonance Imaging (fMRI) was acquired from adolescent patients before CBT, and 24-weeks later following completed therapy. Similar data were obtained from control participants. *Cross-sectional Cohort*: From 82 patients and 34 controls at baseline, rsFC of the amygdala, anterior cingulate cortex (ACC), and pre-frontal cortex (PFC) was calculated for comparison. *Longitudinal Cohort*: From 17 patients and 30 controls with longitudinal data, treatment effects were tested on rsFC. Patients demonstrated significantly greater rsFC to left amygdala, bilateral supragenual ACC, but not with PFC. Treatment effects were observed in right insula connected to left supragenual ACC, with baseline case-control differences reduced. rsFC changes were significantly correlated with changes in depression severity. Depressed adolescents exhibited heightened connectivity in regions of 'hot' emotional processing, known to be associated with depression, where treatment exposure exerted positive effects, without concomitant differences in areas of 'cold' cognition.

© 2017 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Major depressive disorder (MDD) is a leading cause of disability (Whiteford et al., 2015). Amongst adolescents, point prevalence is 6–9% (Reivich et al., 2013), with a 25% lifetime prevalence by the end of adolescence (Kessler et al., 2001). Depressed adolescents demonstrate concurrent functional impairments in cognitive and social areas, and high rates of personality disorders, suicide, self-harm, and substance abuse (Harrington, 2001). Around 33% of diagnosed adult cases originate in adolescence (Goodyer et al., 2011). MDD can arise during adolescence from psychosocial stress factors, differences in epigenetic and genetic susceptibilities, and glucocorticoid vulnerabilities that lead separately or in combination to imbalances between bottom-up emotional

('hot') processing and top-down cognitive ('cold') processing, triggering lasting alterations in brain maturation trajectories (Hagan et al., 2015).

Blood oxygenation level dependent (BOLD) sensitive functional magnetic resonance imaging (fMRI) acquired during stimuli-free acquisition is the basis for constructing resting state functional connectivity (rsFC) networks of synchronous, spontaneous brain activity. Evidence from fMRI in depressed adults provides strong support for disruption of the fronto-limbic system, a key component of the 'hot' emotional processing system (Anand et al., 2009). However, the ACC has also been implicated in 'cold' cognition (Shackman et al., 2011). Specifically, MDD is associated with dysfunction of the anterior cingulate cortex (ACC)-pallidostriatal-thalamic-amygdala circuit, which forms part of the cortico-limbic mood-regulating circuit (Anand et al., 2009), with increased subgenual ACC (sgACC)-default mode network (DMN) and thalamus-DMN rsFC in patients (Greicius et al., 2007). Adolescent patients also demonstrate increased sgACC-insula, and sgACC-amygdala rsFC (Connolly et al., 2013).

* Corresponding author at: Department of Psychiatry, University of Cambridge, Herchel Smith Building for Brain and Mind Sciences, Robinson Way, Cambridge CB2 0S2, UK.
E-mail address: sc751@cam.ac.uk (S. Chattopadhyay).

<http://dx.doi.org/10.1016/j.ebiom.2017.02.010>

2352-3964/© 2017 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Please cite this article as: Chattopadhyay, S., et al., Cognitive Behavioral Therapy Lowers Elevated Functional Connectivity in Depressed Adolescents, EBioMedicine (2017), <http://dx.doi.org/10.1016/j.ebiom.2017.02.010>

A corresponding decrease in areas involved in ‘cold’ cognitive control, such as the PFC, is seen in adult patients (Anand et al., 2005). Reduced rsFC has also been detected in the ACC, insula, amygdala, and frontal pole (Veer et al., 2010). Whether these connectivity findings are present in adolescents with MDD is less clear, although adolescent patients have exhibited decreased rsFC between sgACC and supragenual ACC, insula, and parts of the frontal and temporal cortices (Cullen et al., 2009). Given that diagnostic characteristics are the same across all ages, we hypothesise that these findings will be replicated in this young age range prior to treatment.

National Institute for Health and Care Excellence (NICE) guidelines in the United Kingdom for the treatment of depression in adolescence recommend psychological therapies such as cognitive behavioral therapy (CBT) as first-line treatment, with or without the antidepressant fluoxetine (NICE, 2015). There is evidence from imaging that either treatment is associated with restoring fronto-limbic connectivity in adults (Gudayol-Ferré et al., 2015).

This study is an analysis of rsFC in adolescent patients with MDD enrolled in the Improving Mood with Psychoanalytic and Cognitive Therapies (IMPACT) clinical trial (Goodyer et al., 2011). As MDD is associated with pathological increases in physiological activity in regions of ‘hot’ emotional processing, and reduced in activity in regions of ‘cold’ cognitive control, we hypothesized that, prior to treatment with CBT, adolescent MDD patients would show hyper-connectivity in limbic structures and hypo-connectivity in regions connected to the pre-frontal cortex. We further hypothesized that CBT would be associated with normalising rsFC patterns in patients towards those seen in controls. Ameliorating aberrant connectivity associated with depressive illness early in the course of the disorder may pre-empt more atypical developmental changes to brain structure and related functions, thereby reducing the risk of recurrence and relapse.

2. Materials and Methods

2.1. Participants

The IMPACT trial was a pragmatic, single-blind, randomized controlled trial with the primary hypothesis that specialised psychological treatments had more enduring clinical effects in maintaining reduced depression symptoms compared with specialist clinical care (Goodyer et al., 2011). Enrolled patients from 16 Child and Adolescent Mental Health Services (CAMHS) clinics in the UK satisfied DSM-IV criteria for unipolar MDD.

The MR-IMPACT study recruited IMPACT participants from East Anglia and North London, and conducted an MRI assessment prior to randomisation (Hagan et al., 2013). Those randomized to CBT were invited to return for a second MRI assessment following completion of their treatment around 24 weeks later (Range of follow-up time for patients: 17.14–51 weeks, standard deviation: 9.27). To be eligible for the post-treatment assessment, participants should have attended at least 6 out of 20 scheduled appointments: median number attended was 8, with a mean interval of 16 days between sessions. Control participants were recruited from local schools and screened for the absence of current depressive illness by requiring a score ≤ 5 on the self-report Short Moods and Feelings Questionnaire (SMFQ) (Sharp et al., 2006). Two MRI assessments were scheduled 24 weeks apart.

The State-Trait Anxiety Inventory (STAI) scale was used to assess current anxiety state using STAI-S and long-term anxiety trait with STAI-T at both MRI assessments (Spielberger et al., 1970), with higher scores indicating greater anxiety levels. Exclusion criteria for all participants included: alcohol or drug dependence, generalized learning problems, pregnancy or breastfeeding, concurrent medication use that could adversely interact with SSRIs (patients only), and MRI contraindications (Hagan et al., 2013). Participants and their families gave signed informed consent. Ethical approval was provided by the Cambridgeshire

2 Research Ethics Committee (Reference: 09-H0308-168), following the Declaration of Helsinki.

In total, 168 participants 11–17 years old were enrolled into MR-IMPACT: 128 patients (34 males, 94 females) and 40 controls (11 males, 29 females). From these, 108 patients undertook only the pre-treatment (baseline) MRI assessment, of which 26 were excluded, along with 6 controls. Reasons for exclusion are shown in Fig. S1. Thus, 82 patients (18 males, 64 females) and 34 healthy controls (7 males, 27 females) were used for case-control comparisons: this was the *cross-sectional sample* (Table 1).

The 20 remaining patients had both baseline and post-treatment (follow-up) MRI assessments, with 3 excluded (Fig. S1). 33 controls had scans separated by a similar interval, of which 3 were excluded (Fig. S1), leaving 17 patients and 30 controls in the *longitudinal sample* (Table 2). The independence of the patients in the cross-sectional and longitudinal samples is an important feature of the analysis strategy; the *cross-sectional sample* findings were used as a mask for the *longitudinal sample* analyses.

2.2. MRI Acquisition and Processing

MRI scanning took place on a Siemens 3T Trim Trio scanner at the Wolfson Brain Imaging Centre, University of Cambridge, UK. BOLD-sensitive echo-planar images (EPI) were acquired at baseline and follow-up assessments, whilst participants lay awake with eyes closed. EPI scans were 8 min 56 s long with 256 whole-brain images collected. Experimental details were previously published (Hagan et al., 2013).

EPI images were processed to correct for head motion during acquisition using the speedyp algorithm from the BrainWavelet Toolbox (BWT) (www.brainwavelet.org), according to the established protocol (Patel et al., 2014). All data were non-linearly transformed to the standard stereotactic space of the MNI152 template using the Advanced Normalisation Tools (ANTs) (Avants et al., 2009). Once processed, images were overlaid with the Automated Anatomical Labelling (AAL) atlas defining 116 regions of interest (ROIs) (Tzourio-Mazoyer et al., 2002).

Mean DVARS, the average root-mean-square variance across all brain voxels of volume-to-volume difference in percent BOLD signal change, and translations and rotations about orthogonal axes were used to test for between-group differences in head motion using *t*-tests (assuming unequal variances). Eight participants were excluded as their variation of motion exceeded the range $-2 > \text{mean DVARS} > 2$ (Patel et al., 2014).

2.3. Functional Connectivity in ‘Hot’ and ‘Cold’ Systems

Based on previously reported fronto-limbic alterations in depression, amygdala and ACC regions of the AAL atlas were chosen as seed regions to investigate case-control differences in rsFC with the *cross-sectional sample*, as they are those associated with the ‘hot’ emotional system. Bilateral PFC regions corresponding to Brodmann area 9 were chosen as seed regions indicative of the ‘cold’ cognitive system (Fig. 1), based on previous studies (Mayberg et al., 1999). MDD has been associated with specific parts of the ACC (Connolly et al., 2013; Cullen et al., 2009), therefore the ACC was sub-divided into subgenual and supragenual regions, superior and inferior to the line connecting the frontal pole to the genu of the corpus callosum, respectively.

For each seed region separately, using FMRIB’s Software Library’s (FSL’s) FMRI Expert Analysis Tool (FEAT) tool (www.fmrib.ox.ac.uk), a univariate general linear model (GLM) was regressed at each intracerebral voxel, with the average time-series of the seed region as the independent variable and the voxel time-series as the dependent variable, to estimate rsFC with the corresponding *Z*-statistic. Between-group differences in rsFC of the *cross-sectional sample* were tested by GLM across the entire brain parenchyma. For seed regions associated with significant between-group effects, the effect of CBT on the rsFC in the

متن کامل مقاله

دریافت فوری ←

ISIArticles

مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات