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Increases in orbitofrontal cortex thickness following antidepressant treatment are associated with changes in resting state autonomic function in adolescents with major depression – Preliminary findings from a pilot study

Julian Koenig[a,b], Melinda Westlund Schreiner[c], Bonnie Klimes-Dougan[c], Benjamin Ubani[d], Bryon A. Mueller[d], Kelvin O. Lim[d], Michael Kaess[a,b], Kathryn R. Cullen[d,*]

[a] University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Stöckli, Bolligenstrasse 111, 3000, Bern 60, Switzerland
[b] Section for Translational Psychobiology in Child and Adolescent Psychiatry, Department of Child and Adolescent Psychiatry, Centre for Psychosocial Medicine, University of Heidelberg, Blumenstr. 8, 69115, Heidelberg, Germany
[c] Department of Psychology, University of Minnesota, College of Liberal Arts, N218 Elliott Hall, 75 East River Road, Minneapolis, MN, USA
[d] Department of Psychiatry, University of Minnesota, Medical School, F256/2B West Building, 2450 Riverside Avenue, Minneapolis, MN, USA

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ABSTRACT

In adults with major depressive disorder (MDD), effective treatment has been associated with increases in both heart rate variability (HRV) and cortical thickness. However, the impact of treatment on these indices has not yet been examined in adolescents. Cortical thickness and HRV were measured in twelve adolescents with MDD before and after 8 weeks of treatment with a selective serotonin reuptake inhibitor (SSRI). We examined treatment-related changes in depression symptoms, HRV, heart rate (HR), and cortical thickness, and analyzed correlations among these change indices. At follow-up, patients showed significantly decreased depression severity, increased HRV and increased thickness of the left medial orbitofrontal cortex (OFC). Clinical improvement was associated with increased HRV and decreased HR. Increased HRV was associated with increased cortical thickness of left lateral OFC and superior frontal cortex. Due to the small sample size, results represent preliminary findings that need replication. Further, in the absence of a placebo arm, we cannot confirm that the observed effects are due solely to medication. These preliminary findings suggest that SSRI treatment in adolescents impacts both cortical thickness and autonomic functioning. Confirmation of these findings would support OFC thickness and HRV as neurobiological mediators of treatment outcome.

1. Introduction

The vast majority of mental health disorders have their onset during adolescence (Kessler et al., 2007). About 75% of individuals with mental illness experience first symptoms before the age of 25 years (Kessler et al., 2007), with depression being one of the most common mental health problems in adolescents (Merikangas et al., 2009). The developmental neurobiology of major depressive disorder (MDD) is complex and not yet fully understood. MDD has wide-spread effects on neural circuits that mediate emotion and orchestrate a complex array of physiological systems (i.e., autonomic nervous system (ANS), endocrine, and immune systems) (Singh and Gotlib, 2014). Research in adolescents with MDD that integrates the assessment of these multiple intersecting systems will be critical to inform theories of MDD pathogenesis and guide both monitoring and development of treatment. Current knowledge about the neurobiology of MDD is limited as existing models are mostly grounded on cross-sectional evidence. Longitudinal research, such as studies examining treatment-related changes of neurobiological and psychological function in MDD, are essential for advancing knowledge about adolescent MDD.

Research examining heart rate variability (HRV), an index of ANS function that reflects vagal activity, has found that adults (Kemp et al., 2010) and adolescents (Koenig et al., 2016) with MDD tend to have lower HRV than controls (Sgoifo et al., 2015). Furthermore, several previous studies have shown that in adults with MDD, clinical improvement due to treatment is associated with increases in HRV (Balogh et al., 1993; Chambers and Allen, 2002; Glassman et al., 2007; Khaykin et al., 1998). Decrease in depression severity in adults following non-pharmacological treatments such as acupuncture (Chambers and Allen, 2002) or cognitive behavioral therapy

* Corresponding author.
E-mail addresses: julian.koenig@med.uni-heidelberg.de (J. Koenig), Rega0026@umn.edu (K.R. Cullen).

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(Jang et al., 2017) has been associated with an increase of cardiac vagal activity (i.e., indexed by respiratory sinus arrhythmia (RSA), high-frequency HRV (HF-HRV) or the root mean squared difference of successive inter-beat-intervals (RMSSD)) and a decrease in heart rate (HR) (Chambers and Allen, 2002). However, findings from adult depression studies using pharmacological interventions are mixed, with some studies illustrating similar patterns of findings (Balogh et al., 1993; Khaykin et al., 1998) and others showing no significant effects of depression treatment on HRV measures reflecting cardiac vagal activity (Glassman et al., 2007).

Studies addressing the association between clinical improvement and changes in autonomic function in the context of clinical treatment of adolescents are scarce. In community based samples of adolescents, longitudinal associations between vagal activity and difficulties in emotion regulation have been reported, such that lower RSA was associated with and predicted greater difficulties in emotion regulation in annual follow-ups (Vasilev et al., 2009). One of the few longitudinal studies in adolescent patients recently showed that borderline personality disorder (BPD) symptom severity co-varies with HRV and HR in adolescents, such that improvements in BPD symptoms were associated with increases in HRV and decreases in HR (Koenig et al., 2017b). To the best of our knowledge, no prior studies have examined treatment-related changes in HR and HRV in adolescent patients with MDD. Further, the neural mechanisms underlying treatment-related changes in autonomic function are not well understood.

Similar to measures of ANS function, previous research in adults has shown that successful psychotherapy or pharmacological treatment can be accompanied by increases in cortical thickness. A study in adults with treatment-resistant MDD reported increases in cortical thickness of the middle frontal gyrus (MFG), orbitofrontal cortex (OFC), and inferior temporal gyrus following intensive pharmacotherapy in remitters over time (Phillips et al., 2015). Likewise, a study that examined brain structural differences in psychotherapy patients with late-life depression (~73 years) found that in comparison to responders, non-responders showed decreases in cortical thickness in the insular cortices, as well as the right medial OFC, among other regions of interest (ROI; Mackin et al., 2013). Changes in cortical thickness due to treatment may have high clinical significance since greater thickness may be a predictor of future outcomes. For example, in girls at heightened familial risk of depression, those with lower thickness of the OFC, precentral gyrus, anterior cingulate cortex (ACC), and insula were more likely to report depression onset in the subsequent 5 years (Foland-Ross et al., 2015).

While initial lines of research examining cortical thickness and HRV in MDD were conducted separately, more recent integrative studies in healthy subjects have begun to show that HRV is associated with cortical thickness of specific brain regions – suggesting that brain morphology is associated with ANS function (*for a review see* Carnevali et al., 2018). In healthy adults, greater vagally-mediated HRV was associated with greater thickness of the prefrontal cortex (PFC) and ACC (Winkelmann et al., 2016; Wood et al., 2017; Yoo et al., 2017). In contrast, in a sample of healthy adolescents (Koenig et al., 2017a), vagally-mediated HRV was inversely associated with cortical thickness (particularly of the rostral ACC). These contrasting findings suggest that the association between cortical thickness and autonomic function may change as a function of age. However, no prior studies have examined the impact of treatment on autonomic function, cortical thickness and their association with depression severity in adolescents with MDD.

The present study aimed to investigate changes in autonomic function (indexed by resting state HR and time- and frequency-domain measures of HRV) and cortical thickness in adolescents with MDD following 8 weeks of treatment with a selective serotonin reuptake inhibitor (SSRI), and how these changes in neurobiology track with improvement in depression symptoms. In line with previous research, we hypothesized that clinical improvement would be associated with (a) increases in vagally-mediated HRV, (b) decreases in HR, and (c) increases in cortical thickness, predominately in parts of the frontal lobe (MFG and OFC). Further, we aimed to explore co-variance of changes in autonomic function with changes in cortical thickness. We hypothesized that increases in vagally-mediated HRV and decreases in HR would be associated with increases in cortical thickness.

2. Methods

2.1. General procedures

Analyses for the present paper were conducted on data collected from a subsample of a larger study ("Fronto-Limbic Connectivity in Adolescent MDD", PI Cullen). Data for the present study were analyzed using procedures previously described elsewhere; therefore, description of the methods largely overlaps with previous publications (Cullen et al., 2014, 2016; Hall et al., 2014; Klimes-Dougan et al., 2014; Klimes-Dougan et al., 2018). The initial sample of these studies included 17 adolescents aged 12–19 years who were diagnosed with MDD and who completed pre- and post-treatment scans. Pulse oximetry data for six participants was not available (i.e., bad data quality), leaving a total of 12 participants with complete pre- and post-treatment scans and valid HRV data.

The study protocol was approved by the University of Minnesota Institutional Review Board. Recruitment methods included community postings and referrals from local mental health services. MDD participants were eligible to participate if they had a primary diagnosis of MDD and no intake of antidepressant medications in the past two months. Patients were excluded if they endorsed the presence of a neurological or chronic medical condition, mental retardation, pervasive developmental disorder, substance use disorder, bipolar disorder, schizophrenia, or if they had an intelligence quotient (IQ) of less than 80 as determined by the *Wechsler Abbreviated Scale of Intelligence* (WASI; Wechsler, 1999). Participants were also excluded if they had any MRI contraindications such as braces, claustrophobia, or non-MRI safe implants. For the purposes of the present study, participants were selected if they planned to receive 8 weeks of SSRI treatment as recommended by own provider.

2.2. Clinical assessments

Following a phone screen to determine initial eligibility requirements, all participants deemed eligible for participation were invited for an in-person clinical evaluation. Upon arrival to the study site, all participants or their legal guardians (<18 years) provided written informed consent or assent when appropriate. During this visit, all adolescent and parents completed clinical interviews that were conducted separately, which included the *Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version* (K-SADS-PL; Kaufman et al., 1997) and the clinician-administered *Children's Depression Rating Scale - Revised* (CDRS-R; Poznanski et al., 1985). Handedness (*Edinburgh Handedness Inventory;* Oldfield, 1971) was assessed at baseline. Patients provided self-reports on depression severity in the past two weeks using the *Beck Depression Inventory II* (BDI-II; Beck et al., 1996; Osman et al., 2004). At the final visit following 8 weeks of SSRI treatment, participants completed another BDI-II, which was the primary outcome measure of the study.

2.3. Structural neuroimaging

Neuroimaging data were acquired at baseline and after treatment at the Center for Magnetic Resonance Research at UMN using a Siemens 3T TIM Trio scanner and an identical neuroimaging protocol. A five-minute structural scan was acquired using a T1-weighted high-resolution magnetization prepared gradient echo (MPRAGE) sequence: TR = 2530 ms; TE = 3.65 ms; TI = 1100 ms; flip angle = 7°; 1 mm slices, FOV = 256, voxel size 1 × 1 × 1 mm; GRAPPA = 2. FreeSurfer