Resting-State Quantitative Electroencephalography Demonstrates Differential Connectivity in Adolescents with Major Depressive Disorder

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Abstract

Background: Biomarkers for psychiatric disorders in children and adolescents are urgently needed. This cross-sectional pilot study investigated quantitative electroencephalogram (qEEG), a promising intermediate biomarker, in pediatric patients with major depressive disorder (MDD) compared with healthy controls (HCs). We hypothesized that youth with MDD would have increased coherence (connectivity) and absolute alpha power in the frontal cortex compared with HC.

Methods: qEEG was obtained in adolescents aged 14–17 years with MDD ($n = 25$) and age- and gender-matched HCs ($n = 14$). The primary outcome was overall coherence on qEEG in the four frequency bands (alpha, beta, theta, and delta). Other outcomes included frontal-only coherence, overall and frontal-only qEEG power, and clinician-rated measures of anhedonia and anxiety.

Results: Average coherence in the theta band was significantly lower in MDD patients versus HCs, and also lower in frontal cortex among MDD patients. Seven node pairs were significantly different or trending toward significance between MDD and HC; all had lower coherence in MDD patients. Average frontal delta power was significantly higher in MDD versus HCs.

Conclusions: Brain connectivity measured by qEEG differs significantly between adolescents with MDD and HCs. Compared with HCs, youth with MDD showed decreased connectivity, yet no differences in power in any frequency bands. In the frontal cortex, youth with MDD showed decreased resting connectivity in the alpha and theta frequency bands. Impaired development of a resting-state brain network (e.g., default mode network) in adolescents with MDD may represent an intermediate phenotype that can be assessed with qEEG.

Keywords: major depressive disorder, adolescent, qEEG, quantitative electroencephalogram, biomarker, connectivity

Introduction

DEPRESSION AFFECTS UP TO 20% of children and adolescents (Mendelson and Tandon 2016). Children suffering from major depressive disorder (MDD) are at risk of suicide, self-injury, substance use disorders, and poor school performance (Kupfer et al. 2012). Adolescents with MDD are at risk of future psychiatric disorders and chronic health conditions (Kupfer et al. 2012).

Early recognition, accurate diagnosis, and prognosis determination that could help guide treatment of MDD in youth is challenging. Imprecise nosology and overlapping presentations are particularly common in child psychiatry (Mendelson and Tandon

2016), and there are no well-established biomarkers for psychiatric illness. Many biomarkers are being investigated, ranging from genetic markers to active markers of disease, including, but not limited to, neurotransmitter levels, markers of inflammation, and markers of oxidative stress (Kim et al. 2014). In this aim, “intermediate phenotype” measurements that lie on a continuum between genetics and clinical symptoms (Leuchter et al. 2014) can serve as biomarkers for complex illnesses such as depression and other psychiatric disorders (Leuchter et al. 2014).

Quantitative electroencephalogram (qEEG), the computational processing of digitally acquired EEG signals, has emerged as a possible intermediate biomarker in MDD (Olbrich and Arns 2013).

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Measures of neural connectivity have been studied with qEEG in MDD (Jiang et al. 2016). One qEEG metric, oscillatory synchrony (OS, also called coherence or connectivity), assesses neural connectivity, a quantification of neuronal firing in unison. Studies in adults with MDD showed increased resting OS compared with healthy controls (HCs), most consistently in the prefrontal cortex (PFC) (Leuchter et al. 2014; Olbrich et al. 2014). Increased resting OS may reflect a diminished modulatory capacity of the brain in MDD. In other words, neurons in the brains of depressed adults may be firing in “lock step” in such a way that makes it difficult for the depressed brain to respond to external stimuli (Olbrich et al. 2015).

In addition to neural connectivity, qEEG measures of power in several frequency bands have also been associated with MDD and treatment response (Arns et al. 2015; Pizzagalli et al. 2018). For example, several studies have found increased resting alpha wave activity in depressed subjects versus HCs, most pronounced in the frontal electrodes (Arns and Olbrich 2014; Olbrich et al. 2015). However, some smaller studies have seen decreased absolute alpha power in MDD subjects compared with controls (Jiang et al. 2016). Measures of power, or overall activity in qEEG, have been studied as a marker of treatment response and a possible prognostic indicator in MDD (Widge et al. 2018).

While data have accumulated on the use of qEEG as a marker for adult psychiatric illness and treatment response, no data are available on pediatric MDD and qEEG to date. The thalamocortical theory of MDD supports the possibility that qEEG changes seen in adults and children may be similar. Neurons projecting from the thalamus to the cortex primarily secrete serotonin as a neurotransmitter (Penner et al. 2016). In children and adolescents, serotonergic treatments have been the primary psychopharmacologic strategy in treating childhood-onset MDD. However, substantial data also suggest that the neurophysiology of MDD in children is different from adults (Miller et al. 2015; Schmaal et al. 2017). Miller et al. reported that youth with MDD demonstrated higher activity in prefrontal cortical regions, particularly in response to negative stimuli. This is in contrast to adult data that typically found lower activity in these regions in MDD compared with HCs (Hamilton et al. 2012). To date, there has been very limited research on MDD symptom subtypes in youth and no qEEG studies investigating MDD subtypes in children (Lamers et al. 2012).

This cross-sectional comparative pilot study investigated brain region connectivity using qEEG in youth with MDD versus HCs. We hypothesized that youth with MDD would have increased coherence (connectivity) and absolute alpha power in the frontopolar midline region versus HCs. Additional exploratory analyses investigated whether depressive symptom type and severity is associated with qEEG measures.

Overall study description

This study enrolled 40 adolescents aged 14–17 (25 with MDD and 15 age- and gender-matched HCs). Clinical assessments included a diagnostic evaluation and standardized measures of depression, anhedonia, and anxiety, as well as medication treatments. Each participant completed assessments in one visit or returned within 1 week to complete the qEEG. The primary outcome was coherence on qEEG in MDD cases versus HCs. Secondary analyses assessed qEEG power and subtypes of pediatric MDD (anxious) on qEEG parameters.

Subjects and recruitment

MDD participants were referred from clinical providers within the department of psychiatry at an urban outpatient clinic. Inclusion

criteria for MDD cases were: (1) DSM-5 criteria for MDD based on clinical evaluation by a child psychiatrist, (2) confirmed MDD diagnosis by MINI-KID (Sheehan et al. 1998), and (3) at least moderate MDD severity, defined by a Children’s Depression Rating Scale (CDRS) score ≥ 40 . Exclusion criteria were: (1) current or past diagnosis of bipolar disorder or any psychotic disorder, (2) implanted shunts, (3) prior brain surgery, (4) history of seizure disorder with the exception of febrile seizures, and (5) meningitis. Additional exclusion criteria for HCs were: (1) no lifetime DSM-4 or DSM-5 psychiatric diagnoses, (2) no first-degree relatives with a history of MDD, bipolar disorder, or psychosis, and (3) no second-degree relatives with a history of bipolar disorder or psychosis. All subjects and their caregivers provided written consent. The study was approved by the local institutional review board.

Measures

Children’s Depression Rating Scale–Revised

MDD severity was assessed with the CDRS–Revised (CDRS-R) (Poznanski and Mokros 1996; Mayes et al. 2010). CDRS-R was originally derived from the Hamilton Depression Rating Scale and is used for children aged 6–17 (Poznanski and Mokros 1996). It is a 17-item scale, with items ranging from 1 to 5 or 1 to 7; total possible scores range from 17 to 113. A cut-off score ≤ 28 equates to minimal or no symptoms of depression, whereas a score ≥ 40 indicates clinically significant depression.

Snaith-Hamilton Pleasure Scale

The Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith 1993) assesses anhedonia or the inability to experience pleasure in normally pleasant experiences. SHAPS has 14 self-report Likert-scale items with the option to choose *strongly disagree*, *disagree*, *agree*, or *strongly agree* for each item. When scoring, each “disagree” endorsement is given 1 point and each “agree” endorsement is given 0 point. Total scores range from 0 to 14, with higher scores indicating higher anhedonia.

Pediatric Anxiety Rating Scale

Anxiety was assessed with the Pediatric Anxiety Rating Scale (PARS) (Riddle et al. 2002), a 50-item symptom checklist of items grouped into categories of: Social Interactions or Performance Situations (9 items), Separation (10 items), Generalized (8 items), Specific Phobia (4 items), Physical Signs and Symptoms (13 items), and Other (6 items). Symptoms are scored on seven dimensions of severity, using a six-point scale (0 for none, and 1–5 for minimal to extreme) for each dimension, and these are added to get a total score. Total scores range from 0 to 35, with higher scores indicating higher severity of anxiety. A score ≥ 10 indicates clinically significant anxiety, and scores ≥ 20 indicate severe anxiety (Riddle et al. 2002).

EEG data collection. EEG data were acquired using a Discovery 24 EEG amplifier, which has been approved by the U.S. Food and Drug Administration. Resting EEGs were recorded while subjects lay quietly with their eyes closed in a sound-attenuated room. Subjects were alerted frequently to avoid drowsiness and were instructed to remain still and inhibit blinks or eye movements during each recording period. EEGs were recorded using a 32-channel enhanced version of the International 10–20 System of Electrode Placement (Supplementary Fig. S1), using the montage in Supplementary Figure S2.

qEEG analysis. We developed a semi-automatic tool to compute the power spectral density (PSD) and coherence measures for each subject (Fig. 1).

The tool allows the user to open an EEG study for review and verification of EEG segments before calculating the PSD and coherence measures. The default segment length was set at 2 seconds for analysis, and the tool automatically analyzed the six eye channels (LOC-LSO, LOC-LIO, LSO-LIO, ROC-RSO, ROC-RIO, RSO-RIO) to detect segments with eye movements. Eye movement detection was based on the magnitude of signals in the six EEG channels after filtering the data for clinical review. The EEG data for each subject were reviewed in a semi-automated process involving both clinician review and automated removal of segments containing artifacts. Upon completing the semi-automated review process, PSD and coherence were calculated for the selected EEG channels and for the delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–20 Hz) frequency bands.

See Supplementary Data for details of calculation of power and coherence.

Data Analysis

Demographic information is presented in Table 1, and comorbid diagnoses and concomitant medication information are presented in Table 2.

Primary outcome analyses: coherence

From the above calculations, the data for each frequency band within each electrode pair were averaged across all epochs for each participant (e.g., F7–T7 alpha, F7–T7 beta, etc.) for coherence. Additionally, the four node pairs that lay completely within the frontal region of the brain were averaged to calculate average frontal coherence. These node pairs were: Fp1–F7, Fp2–F8, Fp1–F3, Fp2–F4. Lastly, overall coherence was calculated by taking coherence measurements across all locations of the brain, parsed out by each frequency band (e.g., average delta coherence, average theta power).

Overall coherence measurements for each frequency band were compared between MDD and HC with two-tailed *t*-tests. Similarly, each node pair was assessed for differences between groups with *t*-tests for each frequency band, as well as the average frontal-only measurements. Type I error level of 0.05 was assumed, and all coherence data were normally distributed.

Spearman correlations were computed to determine whether the severity of depression (as measured by CDRS-R) was associated with qEEG coherence values for each frequency band overall and also in the frontal area only. CDRS-R data were non-normal due to the minimal severity of depression symptoms for HCs and extreme depression symptoms for youth with MDD.

Secondary outcome analyses: power

Similar methods for primary outcome analyses were run for power as coherence: power of each frequency band for each electrode pair, frontal-only power for each frequency band, and overall power for each frequency band. Power data were normally distributed across the sample.

Exploratory analyses

Overall sample. Spearman correlations were run to determine whether severity of anhedonia (as measured by SHAPS) and severity of anxiety (as measured by PARS) created a difference in qEEG coherence values for each frequency band overall and also in the frontal-only area. Similar to CDRS-R, these scales also yielded non-normal data, resulting in the need for nonparametric tests.

Since two participants with MDD were not taking any medications, we removed them from the sample and re-ran the statistics to determine if the difference in coherence between youth with MDD and HCs remained significant across frequency bands.

MDD sample only. The sample was then split to analyze differences between MDD subjects only. Two-tailed *t*-tests were run to determine whether there was a significant difference in average

FIG. 1. Quantitative EEG analysis tool. EEG, electroencephalography.

TABLE 1. DEMOGRAPHICS OF OVERALL SAMPLE SPLIT BY MENTAL HEALTH CONDITION

	MDD, n = 25	HCS, n = 15	Statistics
Age, mean (SD)	15.96 (0.94)	15.40 (0.99)	$t(38) = 1.80, p = 0.08$
Female, N (%)	20 (80.0)	11 (73.3)	$p = 0.71$ (Fisher's exact)
Race			
Caucasian	21 (84.0)	13 (86.7)	$\chi^2(2) = 0.62, p = 0.73$
African American	3 (12.0)	2 (13.3)	
Asian	1 (4.0)	0 (0.0)	
SHAPS ^{a,b} total score, mean (SD), range	28.55 (6.36), 18–39, n = 20	19.27 (3.59), 14–28, n = 15	$t(31) = 5.47, p < 0.001$
CDRS-R ^c total score, mean (SD), range	65.92 (11.03), 44–85	18.54 (2.59), 17–27	$t(28.2) = 29.55, p < 0.001$
PARS ^d total score, mean (SD), range	22.9 (6.60), 2–33	1.80 (3.23), 0–10	$t(38) = 11.55, p < 0.001$

^aTotal scores range from 0 to 14, with higher scores indicating higher anhedonia.

^bIntroduced to the study after five people already completed.

^cTotal scores range from 17 to 113, with higher scores indicating higher depression.

^dTotal scores range from 0 to 35, with higher scores indicating higher severity of anxiety.

CDRS-R, Children's Depression Rating Scale-Revised; HC, healthy control; MDD, major depressive disorder; PARS, Pediatric Anxiety Rating Scale; SHAPS, Snaith-Hamilton Pleasure Scale.

mean coherence for those taking medications compared with those not taking medications. This was run using overall coherence averages and frontal-only averages for each frequency band.

Additionally, two-tailed *t*-tests were applied to determine the difference in average coherence levels between MDD subjects taking selective serotonin reuptake inhibitors (SSRIs) only ($n = 7$) and those not taking any medication ($n = 2$) for both overall regions as well as the frontal-only regions.

Two-tailed *t*-tests were also run to determine the difference in average overall coherence levels and average frontal coherence levels between MDD subjects taking an antidepressant and those not taking any medications. SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors, and tetracyclic antidepressants were classified as antidepressants, and were limited to these categories as these were the only types of antidepressants the subjects were taking.

Results

Overall sample results

Average age was 15.76 years (standard deviation [SD] = 0.99); 77.5% were females and 85% were white. See Table 1 for demographics and measured scores by experimental group.

Coherence

Overall, average coherence in the theta band was significantly lower for the MDD cohort (mean = 0.60, SD = 0.03) compared with HCs (mean = 0.61, SD = 0.02; $t(38) = -2.93, p = 0.049$), but was not significant in any other frequency band.

Similarly, the theta band was the only frequency band with significantly lower coherence in the frontal-only area (MDD mean = 0.68, SD = 0.04; HC mean = 0.70, SD = 0.05; $t(38) = -2.07, p = 0.046$).

There are seven node pairs that were significantly different or trending toward significance between youth with MDD and HCs; all had lower coherence in the MDD cohort. See Figure 2 for a diagram of the specific significant node pairs regarding coherence.

Depressive symptom correlations

There was a significant correlation between depressive symptom severity (CDRS-R total score) and average alpha coherence

$[r_s(38) = -0.35, p = 0.03, 95\% \text{ CI} = -0.61 \text{ to } -0.02]$. Additionally, there was a significant correlation between average theta coherence and severity of depression $[r_s(38) = -0.35, p = 0.03, 95\% \text{ CI} = -0.57 \text{ to } -0.04]$, but no significant correlation with average delta coherence or average beta coherence.

Comparably, CDRS-R total score and average frontal alpha coherence and average frontal theta coherence were significantly correlated $[r_s(38) = -0.40, p = 0.01, 95\% \text{ CI} = -0.65 \text{ to } -0.06; r_s(38) = -0.38, p = 0.01, 95\% \text{ CI} = -0.61 \text{ to } -0.08]$, respectively, but the average frontal delta coherence or average frontal beta coherence was not correlated.

Anhedonia symptom correlations

Similar to depression, there was a significant correlation between severity of anhedonia (SHAPS total score) and average alpha coherence $[r_s(33) = -0.41, p = 0.014, 95\% \text{ CI} = -0.70 \text{ to } -0.07]$, but no significant correlation between SHAPS total score and average delta coherence, average theta coherence, or average beta coherence.

The SHAPS total score significantly correlated with average frontal alpha coherence $[r_s(38) = -0.48, p < 0.01, 95\% \text{ CI} = -0.69 \text{ to } -0.19]$, average frontal theta coherence $[r_s(38) = -0.40, p = 0.02, 95\% \text{ CI} = -0.65 \text{ to } -0.06]$, and average frontal beta coherence $[r_s(38) = -0.35, p = 0.04, 95\% \text{ CI} = -0.59 \text{ to } -0.02]$. There was no significant correlation with severity of anhedonia and average frontal delta coherence.

Anxiety symptom correlations

Similar to depression and anhedonia, there was a significant correlation between severity of anxiety (PARS total score) and average alpha coherence $[r_s(38) = -0.32, p = 0.047, 95\% \text{ CI} = -0.60 \text{ to } 0.003]$, but no significant correlation between PARS total score and average delta coherence, average theta coherence, or average beta coherence.

The PARS total score significantly correlated with the average frontal alpha coherence and average frontal theta coherence $[r_s(38) = -0.38, p = 0.02, 95\% \text{ CI} = -0.64 \text{ to } -0.07; r_s(38) = -0.38, p = 0.02, 95\% \text{ CI} = -0.64 \text{ to } -0.03]$, respectively. There was no significant correlation between anxiety severity and average frontal beta coherence or average frontal delta coherence.

TABLE 2. CLINICAL CHARACTERISTICS OF ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER (N=25)

	N (%)
PARS total scores	
0–9 (no anxiety)	1 (4.0)
10–19 (clinically significant anxiety)	3 (12.0)
20+ (Severe anxiety)	21 (84.0)
No. of comorbid diagnosis, mean (SD), range, median	3.80 (2.29), 0–9, 3.00
Suicidality, as defined by MINI scores Risk	14 (56.0)
No risk (0 points)	11 (44.0)
Low (1–5 points)	5 (35.7)
Medium (6–9 points)	5 (35.7)
High (10+ points)	4 (28.6)
Comorbid diagnoses	
Anxiety disorders ^a	20 (80.0)
Externalizing disorders ^b	6 (24.0)
Concomitant medications	23 (57.5)
Antidepressant indication only	10 (40.0)
Mean no. of MDD meds (SD), range, median	1.10 (0.32), 1–2, 1.00
Anxiety indication only	6 (24.0)
Mean no. of anxiety meds (SD), range, median	1.33 (0.52), 1–2, 1.00
Antidepressant and anxiety combined	18 (72.0)
Mean no. of MDD/anxiety meds (SD), range, median	1.00 (0.00), 1–1, 1.00
ADHD indication	7 (28.0)
Mean no. of ADHD meds (SD), range, median	1.14 (0.38), 1–2, 1.00
Melatonin	1 (4.0)
No. of concomitant meds, mean (SD), range, median	1.84 (1.18), 0–5, 2.00
Concomitant medication classes	
Stimulant	5 (20.0)
α_2 agonist	3 (12.0)
Benzodiazepine	2 (8.0)
SNRI	3 (12.0)
Histamine antagonist	4 (16.0)
SSRI	14 (56.0)
Mood stabilizer	2 (8.0)
Sleep aid (melatonin)	1 (4.0)
SARI	2 (8.0)
α_1 antagonist	1 (4.0)
β blocker	1 (4.0)
Tetracyclic/tycyclic antidepressant	2 (8.0)
NDRI	4 (16.0)
No. of classifications of concomitant medications	
0	2 (8.0)
1	10 (40.0)
2	8 (32.0)
3	3 (12.0)
4	1 (4.0)
5	1 (4.0)

^aClassified as having at least one of the following: generalized anxiety disorder, panic disorder, agoraphobia, social anxiety, obsessive-compulsive disorder, specific phobia.

^bClassified as having ADHD and/or conduct disorder.

ADHD, attention-deficit/hyperactivity disorder; MDD, major depressive disorder; NDRI, norepinephrine-dopamine reuptake inhibitor; PARS, Pediatric Anxiety Rating Scale; SARI, serotonin antagonist and reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Power

Overall, average power did not significantly differ on any frequency bands between youth with MDD and HCs (all p -values >0.11).

The average frontal delta power was significantly higher [$t(38)=2.58, p=0.014$] in youth with MDD (mean=3.09, SD=0.76) than HCs (mean=2.45, SD=0.74). Additionally, the average frontal beta power was higher in MDD youth (mean=0.39, SD=0.72) compared with HC (mean=0.34, SD=0.08), but not reaching statistical significance [$t(38)=2.01, p=0.051$].

There are 17 node pairs that significantly differed or trended toward significance for power between youth with MDD and HCs. See Figure 3 for the specific significant pairs regarding power. Out of the four node pairs where delta waves were significant, each MDD value was higher than HC. Similarly, the two significant beta waves were higher for the MDD cohort. All eight significant power values in the theta wave and all three significant power values in the alpha wave were lower for youth with MDD compared to HCs.

Frontal coherence continued to be significantly lower for the MDD cohort than HCs when the two unmedicated depressed youth were removed from the sample; the alpha band was significantly lower for youth with MDD than HCs and the theta band was trending toward significance.

MDD-only results

Two MDD participants (8%) were not taking any concomitant medications. There were no significant differences in overall coherence in any of the band waves between MDD participants taking medication versus unmedicated. However, there was a trend in average coherence in the frontal alpha wave band to be lower in those taking medications (mean=0.70, SD=0.07, $n=23$) versus unmedicated (mean=0.80, SD=0.01; $t(23)=1.99, p=0.058, n=2$).

There were no significant differences found in any frequency bands for overall coherence when looking at those taking an

FIG. 2. Bipolar nodes and frequencies where coherence is significantly lower in MDD cohort compared with HCs. — refers to delta; --- refers to theta; == refers to alpha; ■■ refers to beta. HC, healthy control; MDD, major depressive disorder.

FIG. 3. Bipolar nodes showing significant differences in power measurements between MDD cohort and HCs. — refers to delta; --- refers to theta; == refers to alpha; ■■ refers to beta. HC, healthy control; MDD, major depressive disorder.

antidepressant and those not taking any medications. However, the average frontal alpha coherence trended toward a significant difference when comparing those on an antidepressant (mean = 0.70, SD = 0.07) versus unmedicated (mean = 0.67, SD = 0.001; $t(19) = 1.92$, $p = 0.07$).

Discussion

Examining the potential biomarkers for MDD in adolescents is critical for understanding the underlying biologic mechanisms driving depression in youth, as well as the effects of depression on the developing adolescent brain. This pilot study suggests that qEEG may be a potential biomarker for depression in youth. In contrast to our initial hypothesis, we demonstrated lower coherence, a measure of functional connectivity, in youth with MDD compared with HCs.

In adults, qEEG measurements in MDD seem to suggest that neuronal firing is abnormally synchronous “marching in lock-step,” which could perhaps explain some of the difficulties that depressed adults have in responding to external stimuli (amotivation, anhedonia) and perhaps also drive the development of cognitive deficits. In contrast to adult qEEG studies in MDD, our study found lower whole-brain coherence in the theta frequency band in depressed youth compared with HCs. In addition, the frontal cortex showed lower functional connectivity in theta frequency in depressed youth compared with HCs in our sample. Specific nodes representing the right PFC and the left parietal cortex also showed lower connectivity in multiple frequency bands (delta, theta, and alpha) in youth with MDD compared with HCs.

It is well established that adolescence is a time of significant pruning and brain development, and that the types and strength of neural connections do not appear similar to an adult brain until the age of at least 25 (Marsh et al. 2008). There are a variety of considerations that could account for the asynchronous activity of “marching to the beat of their own drum” seen in our sample of MDD youth. Since the qEEGs were recorded while our subjects were awake with eyes closed, we can conclude that brain activity is

not being driven by a specific task, but rather by the brain’s intrinsic resting activity. This has been hypothesized in other studies to represent the workings of the default mode network (DMN) (Raichle 2015), consisting of functionally connected regions of the brain whose activity increases during “rest” and decreases during directed or task-oriented mental states (Buckner et al. 2008). The areas of the brain most consistently implicated as being core components of the DMN are: the ventral medial PFC, the dorsal medial PFC, and the posterior cingulate cortex (PCC) (Raichle 2015). Our results showed lower coherence in the right PFC of depressed youth, which may correspond to the frontal “hub” of the DMN. In addition, in the left occipital cortex, MDD youth demonstrated lower coherence compared with HCs. This was seen in the theta and alpha frequency bands of the qEEG. There is some preliminary data that combines functional imaging and qEEG, suggesting that theta band frequencies in the frontal lobe and the alpha band frequencies in the occipital lobe may correspond to resting networks measured in functional imaging (Nishida et al. 2015), suggesting that the difference we observed in the connectivity in depressed youth may be representative of the DMN.

With regard to the development of brain through childhood and adolescence, connectivity between the mPFC and the PCC changes during this time, and there is evidence that coherence between the mPFC and PCC is weaker during childhood and solidifies during adolescence (Dennis and Thompson 2014). It is thus possible that lower connectivity (measured by coherence) in MDD youth, as seen in our study, indicates delayed maturation of the DMN in MDD adolescents. This is consistent with prior research identifying altered resting state connectivity in the DMN in youth with MDD (Cullen et al. 2009; Hulvershorn et al. 2011; Ho et al. 2015).

Our results did not find any difference in global resting power between depressed youth and HCs in any frequency bands. In contrast to our initial hypothesis, we also did not find a significant difference in alpha power in the frontal lobes between depressed youth and HCs. Differences in power in other frequency bands, however, were seen between depressed youth and HCs. Specifically, depressed youths had lower theta power bilaterally in the parietal and occipital cortex compared with HCs. Though previous studies in adults have investigated theta power as a possible prognostic indicator in MDD (Pizzagalli et al. 2018), these studies have focused on theta power in the anterior cingulate cortex, and our sample showed differences in the parietal and occipital cortex. This difference may represent a developmental difference in youth with MDD, which requires further investigation in future studies.

In addition to the primary outcome of interest, we looked at interactions between comorbid symptoms and qEEG. Subtypes of MDD, including MDD with significant anxiety and MDD with significant anhedonia, have had growing research in adults (van Loo et al. 2012) but limited research in youth. In our sample, both anxiety and anhedonia severity were correlated with lower frontal alpha and theta connectivity. However, nearly all of the depressed youth in our study had significant levels of anxiety and anhedonia, making it difficult to assess differential EEG outcomes along a full spectrum of anxiety or anhedonia symptoms.

With respect to medication and symptom subtypes, there was a trend for medicated youth to show lower alpha band connectivity in the PFC compared with unmedicated youth. However, only two youth were not taking medication, and it thus remains unclear if this trend may be a function of medication or an indication of illness severity. Previous adult studies have shown that a reduction in frontal connectivity is a predictor of treatment response with SSRIs and SNRIs (Cook et al. 2002; Bares et al. 2008, 2010; Widge et al.

2018), and that the theta band is most consistently predictive of antidepressant response, rather than the alpha band as seen in our data (Cook et al. 2002; Bares et al. 2008, 2010).

Limitations and Questions for Further Study

Limitations to our findings include the small sample size, cross-sectional design, racial homogeneity, and underrepresentation of males. Multiple comparisons adjustments were not conducted for the analyses in this study, due to its novel and exploratory nature. All but two of the MDD subjects were on psychotropic medication, including SSRIs, mood stabilizers, and stimulants. Since only two MDD participants were not taking any medication, we were not able to adequately explore the difference between medicated and unmedicated depressed youth. Thus, our findings may not be generalizable to the full spectrum of MDD youth. Furthermore, EEG has limited spatial resolution, and research is in the early stages comparing resting-state EEG data with functional imaging data (Nishida et al. 2015). A significant question that remains is whether the resting-state network as measured by qEEG is, in fact, the DMN typically described in functional imaging research. In spite of these limitations, this study is, to the best of our knowledge, a first-ever qEEG analysis of MDD youth. Our future studies will address the described limitations and also seek to correlate findings with additional biomarkers, such as functional neuroimaging.

Conclusions

Brain connectivity measured by qEEG differs significantly between MDD youth and HCs. Overall, youth with MDD showed decreased coherence in the theta band and no differences in power in any of the four frequency bands compared with HCs. When focusing on frontal regions, MDD youth showed decreased resting connectivity in the alpha and theta frequency bands.

This pilot suggests the potential of using qEEG as an intermediate biomarker for MDD.

Clinical Significance

qEEG may represent a feasible tool to assess adolescents with MDD. Youth with MDD showed decreased connectivity on qEEG compared with HCs, but further research is needed before incorporating qEEG as a part of routine clinical practice. qEEG was well tolerated by youth with MDD and, if further research confirms abnormal connectivity in MDD, qEEG could represent a low-cost biomarker to supplement the current assessment tools.

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Supplementary Material

Supplementary Data
Supplementary Figure S1
Supplementary Figure S2

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