A pilot resting-state functional connectivity study of the kynurenine pathway in adolescents with depression and healthy controls

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ABSTRACT

Background: The neuroimmunological kynurenine pathway (KP) has been hypothesized to play a role in depressive/anhedonic symptoms and related CNS disturbances. Indoleamine 2,3-dioxygenase (IDO) is the rate limiting enzyme which leads to neurotrophic [kynurenic acid (KA)] and neurotoxic [Quinolinic acid (QUIN)] branches. In this pilot, we sought to examine associations between blood KP neuro-toxic/trophic measures and anhedonia/depression associated networks in youth with major depression (MDD) and healthy controls (HC).

Methods: Subjects were 14 psychotropic-medication free adolescents with MDD and 7 HC, ages 12–19 yo. All underwent resting-state functional magnetic resonance imaging (fMRI) scans. Voxel-wise maps were generated indicating correlation strengths among 4 bilateral seeds [(dorsal anterior cingulate cortex (dACC), perigenual ACC (pgACC), subgenual ACC (sgACC) and nucleus accumbens (NAc)] and remaining brain regions. FMRI analyses were family-wise error corrected. KP metabolites were measured using liquid chromatography–tandem mass spectrometry.

Results: Connectivity between the right dACC and the right precuneus was positively correlated with KA levels. This same cluster demonstrated an inverse correlation with IDO activity. Exploratory analysis at a more liberal clustering threshold showed the KA/QUIN ratio was positively correlated with connectivity between the pgACC and the right medial prefrontal cortex. Lastly, connectivity between the pgACC and the left inferior temporal gyrus was positively correlated with QUIN levels.

Limitations: Findings are preliminary due to the small sample size.

Conclusions: This pilot study is the first report in depressed adolescents demonstrating associations between the KP and anhedonia/depression-associated brain networks. This pilot adds evidence to the putative role of the KP in MDD.

1. Introduction

Major depressive disorder (MDD) is highly prevalent in adolescence and poses a serious public health concern due to its deleterious outcomes, including increased suicide risk (Asarnow et al., 2008). Furthermore, adolescent MDD is a strong predictor of depression in adulthood (Weissman et al., 1999), which carries a high disability burden (Pine et al., 1999). As such, biological research of adolescent MDD, prior to chronicity effects, is of great importance.

Considerable evidence suggests that activation of the immune system and the release of pro-inflammatory cytokines contribute to the development of major depression in adolescents and adults (Brundin et al., 2016; Gabbay et al., 2010). The kynurenine pathway (KP) has been hypothesized to play a key role in cytokine-induced depressive behaviors and related central nervous system (CNS) disturbances by the production of oxygen free radicals and highly potent neurotoxins (Amori et al., 2009; Schwarz and Pellicciari, 2002). Indoleamine 2,3-dioxygenase (IDO), the rate-limiting enzyme of the KP, is induced by pro-inflammatory cytokines and degrades tryptophan (TRP) into kynurenine (KYN) (Wirleitner et al., 2003). KYN is further metabolized into several neurotoxins, namely 3-hydroxykynurenine (3-HK) and 3-hydroxyanthranilic acid (3-HAA), whose downstream end product is quinolinic acid (QUIN), a glutamatergically-active N-methyl-D-aspartate (NMDA) receptor agonist. Alternately, KYN can also be metabolized into kynurenic acid (KA), a glutamatergic antagonist, producing neuroprotective effects in the brain (Sapko et al., 2006).
Converging data from preclinical and clinical work have implicated the KP in anhedonia, the reduced capacity to experience pleasure. Our laboratory previously documented increased IDO activity (indexed by the KYN/TRP ratio) in adolescents with MDD, but only in those with the melancholic subtype, characterized by anhedonia. We also reported positive associations between KP neurotoxins (KYN, 3-HAA) and increased striatal total choline (a marker for lipid peroxidation) in a group of adolescents with MDD with high levels of anhedonia (Gabbay et al., 2010). Similar findings linking KP activation to anhedonia/MDD symptomatology have also been reported in adults (Anderson et al., 1990; Cowen et al., 1989; Curzon and Bridges, 1970; Maes et al., 1996; Savitz et al., 2015d).

As anhedonia reflects deficits of reward processes (Hasler et al., 2004; Wacker et al., 2009), the above findings suggest the KP may play a role in impairing the neuronal reward circuitry. Relatedly, neuroimaging studies in adults with depression and bipolar disorder documented relationships between blood KP metabolite levels and reward-related brain regions. Findings include associations between IDO activity and striatal volume (Savitz et al., 2015a), KP neurotoxic metabolites and medial PFC cortical thickness (Meier et al., 2016), as well as amygdala and hippocampal volumes (Savitz et al., 2015b, 2015c). Furthermore, ratios of neurotrophic to neurotoxic KP metabolites had distinct associations with hippocampal activation in participants with MDD compared to healthy controls (Young et al., 2016). One prior study also documented distinct associations between both the neurotoxic and neurotrophic branches of the KP and perigenual anterior cingulate cortex (pgACC) network connectivity in a sample of adult football players with and without TBI and healthy controls (Meier et al., 2017). To the best of our knowledge, the latter reference represents the only resting-state study of KP correlates, and there have not been any similar studies in youth or in individuals with depression or other psychiatric disorders.

In the present study, we sought to extend above observations and examine KP blood metabolite levels in relation to whole-brain intrinsic functional connectivity (fIC) of anhedonia-related regions in adolescents with MDD and healthy adolescents. These regions were established based on our prior resting-state functional magnetic resonance imaging (fMRI) study in adolescents with MDD that implicated striatal and salience/reward-related regions (i.e., the dorsal anterior cingulate cortex (dACC) and the subgenual anterior cingulate cortex (sgACC)) in anhedonic symptomatology (Gabbay et al., 2013). In addition, given previous findings that showed associations between the KP and the pgACC connectivity in brain injury, and the significant role of this region in adolescent MDD (Rzepa and McCabe, 2016), we included the pgACC in the current investigation as well. We hypothesized that: 1) neurotrophic factors, such as KA and the KA/QUIN ratio, would be associated with increased whole-brain fIC of our selected regions, demonstrating neuroprotection within the salience/reward network; and 2) conversely, QUIN levels and IDO activity (indexed by the KYN/TRP ratio) would be associated with decreased fIC due to network desegregation via excitotoxicity.

2. Methods

2.1. Study participants

We studied 21 adolescents, 12–19 years old (mean age = 16.68, 15 female), 14 with MDD and 7 healthy controls (HC). Participants represent a subset of subjects from a previously published resting-state study (Gabbay et al., 2013) that had blood samples to be analyzed for KP metabolites. This study was approved by the appropriate Institutional Review Boards. Prior to beginning the study, procedures were explained to parents and participants. Participants 18 years of age or older provided consent, while those under 18 provided assent, and a parent or guardian provided consent.

2.2. Inclusion/exclusion criteria

Participants were excluded if they had any significant medical or neurological disorder, an IQ < 80, claustrophobia, or any MRI contra-indication as assessed by a standard safety screening form. Additionally, a positive urine toxicology test, or a positive urine pregnancy test in females, on the day of the scan were exclusionary. All adolescents with MDD met the DSM-IV-TR criteria for MDD, with a current episode duration ≥ 6 weeks, a raw depression severity score ≥ 40 (T score > 63) on the Children’s Depression Rating Scale–Revised (CDRS-R) (Poznanski et al., 1985), and were psychotropic medication–free for at least 3 months. Exclusionary diagnoses for participants with MDD included a lifetime history of bipolar disorder, schizophrenia, pervasive developmental disorder, panic disorder, obsessive-compulsive disorder, conduct disorder, or Tourette’s disorder. A substance use disorder in the past 12 months was also exclusionary. Lastly, a current diagnosis of posttraumatic stress disorder or an eating disorder were exclusionary. HC participants did not meet criteria for any current or past DSM-IV-TR diagnoses and had never been treated with psychotropic medication.

2.3. Imaging data acquisition

Imaging data were acquired on a 3.0 T Siemens Allegra scanner as previously described in detail (Gabbay et al., 2013). The imaging protocol included a high-resolution T1-weighted magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence (repetition time [TR] = 2500 ms; echo time [TE] = 3.93 ms; inversion time [TI] = 600 ms; flip angle = 8°; 176 slices; voxel size = 1 x 1 x 1 mm³; field of view [FOV] = 256 x 256 mm²) and a resting-state fMRI echo planar imaging (EPI) sequence (197 whole-brain volumes; TR = 2000 ms; effective TE = 25 ms; flip angle = 90°; 39 contiguous 3-mm oblique axial slices parallel to the anterior commissure/posterior commissure line; voxel size = 3 x 3 x 3 mm³; matrix = 64 x 64; FOV = 192 x 192 mm²).

2.4. Imaging data analysis

Data were preprocessed using a combination of C-PAC (Craddock et al., 2013) and AFNI (NIMH Scientific and Statistical Computing Core, Bethesda, MD, US) tools. Preprocessing steps included slice time correction for interleaved slice acquisition, realignment by volume registration, mean-based intensity normalization, and bandpass filtering (0.01–0.1). High resolution anatomical images were transformed into Talairach (TLRC template space) using AFNI’s @auto.tlc, with functional images aligned to this transformed anatomical image using the @auto.tlc linear resampling default option. This was followed by spatial smoothing using 3dBlurtoFWHM in AFNI with a 6 mm full width at half maximum (FWHM) smoothing kernel.

The preprocessed data were regressed on 6 motion parameters. Frame-wise displacement was also calculated across all 197 frames. A scrubbing threshold of 2 mm was used to indicate frames that demonstrated gross frame to frame motion. Resultant maps of scrubbed data did not differ in terms of surviving clusters compared to unscrubbed data; the results reported below include all 197 frames with the original 6 motion parameters regressed out. Seed based correlation maps were then generated and converted to MNI space for group level analysis using AFNI’s 3dwp -tta2mni option.

Bilateral seed regions of interest were selected based on our previous fIC study (Gabbay et al., 2013), including the dACC ([± 16, −6, 44], the sgACC ([± 8, 10, 14], and the nucleus accumbens (NAC; ([± 9, 9 − 8]). Additionally, although our previous study did not include a pgACC seed, this region has been implicated in reward function in adolescent MDD and was thus included here. We used coordinates (0, 38, 0) from a previous study that documented distinct pgACC connectivity patterns associated with decreased ability to anticipate...
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