NeuroImage: Clinical 16 (2017) 604–609

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Structural connectomics of anxious arousal in early adolescence: Translating clinical and ethological findings

Paul B. Sharp*, Eva H. Telzer

University of North Carolina at Chapel Hill, United States

ARTICLE INFO

Keywords:
Connectome
Anxiety
Adolescence
Translational neuroscience
Diffusion imaging

ABSTRACT

Etiological explanations of clinical anxiety can be advanced through understanding the neural mechanisms associated with anxiety in youth prior to the emergence of psychopathology. In this vein, the present study sought to investigate how trait anxiety is related to features of the structural connectome in early adolescence. 40 adolescents (21 female, mean age = 13.49 years) underwent a diffusion-weighted imaging scan. We hypothesized that the strength of several a priori defined structural connections would vary with anxious arousal based on previous work in human clinical neuroscience and adult rodent optogenetics. First, connection strength of caudate to rostral middle frontal gyrus was predicted to be anticorrelated with anxious arousal, predicated on extant work in clinically-diagnosed adolescents. Second, connection strength of amygdala to rostral anterior cingulate and to medial orbital frontal cortex would be positively and negatively correlated with anxious arousal, respectively, predicated on rodent optogenetics showing the former pathway is anxiogenic and the latter is anxiolytic. We also predicted that levels of anxiety would not vary with measures of global network topology, based on reported null findings. Results support that anxiety in early adolescence is associated with (1) the clinical biomarker connecting caudate to frontal cortex, and (2) the anxiogenic pathway connecting amygdala to rostral anterior cingulate, both in left but not right hemisphere. Findings support that in early adolescence, anxious arousal may be related to mechanisms that increase anxiogenesis, and not in a deficit in regulatory mechanisms that support anxiolysis.

1. Introduction

Although it is evident for several biological, psychological and environmental reasons that adolescence is a period of susceptibility for developing psychopathology (Dahl and Hariri, 2005; Telzer et al., 2014), little is known regarding how endogenous and exogenous factors affect relevant neural mechanisms prior to such diseases emerging. To advance knowledge in service of this scientific aim, it is imperative to translate findings and theory from basic neuroscience into hypotheses concerning human development and dysfunction. One such recent, productive endeavor from basic neuroscience, called connectomics, seeks to explicate the structural and functional neural connections across multiple scales of granularity (Sporns, 2012). Indeed, this enterprise has marked a theoretical breakthrough in neuroscience to begin the daunting task of explaining *how* neural ensembles realize psychological functions; that is, to elaborate mechanistic explanations (Thomas and Sharp, under review). Methods used to study the connectome have just begun to be leveraged to investigate psychopathological conditions (Buckholtz and Meyer-Lindenberg, 2012; Van Essen and Barch, 2015). Within this area, little attention has been paid to nonclinical youth, in which such methods could shed light on the developing biology of predisposing emotional traits (Sharp et al., 2015). The present study sought to test if trait anxiety in a nonclinical, early adolescent population was related to features of the structural connectome that have been implicated in basic and applied neuroscience studies on anxiety.

One area that is well suited to advance theory on the mechanisms of human anxiety is ethological work in optogenetics. In this vein, particularly fine-grained insights have recently begun to emerge on the specific connections between amygdala and regions in prefrontal cortex that play causally different roles in anxiety-related behavior. For instance, in rodents, the downstream connection from ventral medial prefrontal cortex (vmPFC) to basomedial amygdala is anxiolytic, whereas basolateral amygdala, primarily connected to dorsal medial prefrontal cortex (dmPFC), promotes freezing behavior under certain conditions (Adhikari et al., 2015). These findings from rodent optogenetics comport with a rich body of literature on the relationship between these two amygdalar pathways and elevated state and trait

* Corresponding author at: 106 Britt Court, Chapel Hill, NC 27514, United States.
E-mail address: psharp89@live.unc.edu (P.B. Sharp).

http://dx.doi.org/10.1016/j.nicl.2017.09.012
Received 17 June 2017; Received in revised form 2 September 2017; Accepted 19 September 2017
Available online 21 September 2017

anxiety in both rodents and human adults. Previous molecular neuroscience work in rodents has identified anterior cingulate-amygdala structural connections being necessary for instantiating anxiety (Bissière et al., 2008; Malin et al., 2007). In healthy adult humans, the structural connectivity between amygdala and dorsal anterior cingulate cortex (part of dmPFC) has been shown to positively covary with trait anxiety (Greening and Mitchell, 2015), whereas the structural connectivity between amygdala and medial OFC (part of vmPFC) negatively covaries with trait anxiety (Greening and Mitchell, 2015; Kim and Whalen, 2009). Moreover, functional MRI studies of human adults have found that amygdala-dmPFC functional connectivity increases as state anxiety is induced (Robinson et al., 2012, 2013, 2014). Taken together, there is support that in both rodents and human adults, the amygdala-dmPFC pathway is involved in anxiogenesis whereas the amygdala-vmPFC pathway is involved in anxiolysis.

Existing literature on the structural biomarkers of trait anxiety in human adolescence specifically, in both clinical and subclinical samples, has generated mixed findings (Gee et al., 2013; Jalbrzikowski et al., 2017; Swartz et al., 2014), with some studies finding connection strength between the amygdala and prefrontal cortex correlating negatively with anxiety (Swartz et al., 2014), whereas others finding positive correlations with anxiety (Jalbrzikowski et al., 2017). Part of the reason for these conflicting findings may be the overreliance on fitting the diffusion tensor model to estimate characteristics of white matter morphology, as is done in analyses focusing on fractional anisotropy. Alternatively, in many connectomics analyses that leverage probabilistic tractography, more complex models (e.g., ball and stick) that do not assume a predominant single fiber direction within a given voxel may yield quite different information. In one of the only studies on adolescent anxiety using the structural connectome approach, adolescents diagnosed with depression and comorbid anxiety, compared to healthy controls, showed reduced connectivity in right caudate to right middle frontal gyrus, but showed no differences in global graph-theoretical measures of network topology (Tymofiyeva et al., 2017). These findings are consistent with work demonstrating that diminished frontostriatal functional connectivity is associated with depression, anxiety, and general deficits in emotion regulation in human adults (Furman et al., 2011; Vaghi et al., 2017) and in human adolescents (Forbes and Dahl, 2012).

It is vital to test whether these neurobiological correlates of trait anxiety manifest in adolescence prior to the emergence of clinically-relevant psychopathology, as the results of such studies can help identify biomarkers of psychological dysfunction that precede disease onset and can inform theories regarding the pathophysiology of the disorder. In the present study, we leveraged diffusion-weighted MRI data to examine how a type of trait anxiety, anxious arousal, is related to changes in the structural connectome in a sample of nonclinical adolescents. Given that anxiety is a broad concept of which there are putative subtypes, we chose to focus on anxious arousal (also called somatic anxiety), as its cluster of symptomatology (lower fear threshold, hypervigilance, sympathetic hyperarousal) is proximal to the phenomena probed in ethological work on which some of our hypotheses were based (e.g., Adhikari et al., 2015; Bissière et al., 2008; Watson et al., 1995). Anxious arousal is conceptualized as a trait measure, given that it has high reliability across time and can predict temporally distal behavior and neural activity (Sharp et al., 2015). By contrast, anxious apprehension is characterized by verbal rumination and worry, two phenomena that qualitatively differ from the more rudimentary anxious phenomenology rodents engage in. Moreover, anxious apprehension includes states marked by rich verbal content, can be about temporally or conceptually distal threats, and engages higher-order cognitive functions (Sharp et al., 2015).

We tested three hypotheses regarding how levels of anxious arousal covary with features of the structural connectome. First, in line with animal work in rodents (e.g., Adhikari et al., 2015), we predicted that anxious arousal would be positively related to connection strength between rostral anterior cingulate cortex (rACC) and amygdala and would be negatively correlated with the connection between medial orbitofrontal cortex (OFC) and amygdala. We focused on rostral anterior cingulate as a homolog of rodent dmPFC (which is defined as the rodent cingulate cortex; Adhikari et al., 2015) due to a convergence across histological, ethological and human neuroscience work in regards to its association with (1) anxiety behavior and phenomenology and (2) connectivity with amygdala (Greening & Mitchell, 2015; Vogt and Paxinos, 2014). Indeed, rACC is positioned between limbic and cortical connections and is critical for amygdala-dependent learning (Bissière et al., 2008). Because of their more precise anatomical designation and because of their nomenclature in the atlas from which we extracted such regions, we will refer to rACC and medial OFC instead of dmPFC and vmPFC, respectively.

Second, we predicted that the same marker of structural connectome dysfunction found in clinically anxious youth (e.g., Tymofiyeva et al., 2017) would bear out in our younger, non-clinical adolescent sample. In particular, we tested whether anxious arousal would be negatively associated with connectivity strength between the caudate to middle frontal gyrus (MFG). Based on previous literature, albeit using diffusion-tensor imaging, we predicted a medium effect size for the relationship between anxiety and the strength of structural neural connections (Baur et al., 2013; Phan et al., 2009). To achieve 80% power, a medium effect between a correlation of 0.3 and 0.4 requires a minimum sample size of 34 participants (Faul et al., 2007).

We also sought to examine whether adolescence is marked by similar focal dysfunction (i.e., specific subnetworks) in the structural connectome as are adults. Connectomes comprise two basic components: nodes and edges. Nodes, in this study, are gray-matter regions defined by the volume, and the edges are the weighted strength of each pathway between nodes. Indeed, extant connectomics literature in adult humans has *not* found significant differences across clinically anxious groups and healthy participants in measures of global network topology (Korgaonkar et al., 2014; Tymofiyeva et al., 2017). These metrics tend to accompany broader dysfunction in cognition, such as the positive symptoms common in schizophrenia (e.g., van den Heuvel et al., 2013). For this reason, we predicted that correlations between global graph-theoretic neural measures (global efficiency, characteristic path length, and node strength) and self-reported anxiety would not be significantly different from the null-hypothesis.

To maximize the sensitivity of our structural connectivity analyses, we employed a model to estimate multiple fibers within each voxel (Behrens et al., 2007). This method is superior to traditional diffusion tensor imaging (DTI) analyses given that DTI studies that derive fractional anisotropy assume each voxel contains one single major fiber direction, which is not the case, as over 90% of voxels contain more than one fiber orientation (Jeurissen et al., 2010). Thus, it is essential to use models that do not assume a predominant single fiber direction within a given voxel.

2. Methods

2.1. Participants

54 adolescents participated in the present study. 14 adolescents were excluded from present analyses due to corrupted diffusion weighted data (see Quality Control section below). Our final sample included 40 adolescents (21 females; mean age = 13.49 years, range = 12.16–14.78 years). All participants completed a phone screen, during which parents confirmed their child had no history of a clinical diagnosis of mental health disorders, were not taking any psychotropic medications, did not have a learning or developmental disability, and were free of all MR contraindications. All participants provided written informed assent and parents provided informed consent which were approved, along with the entire study protocol, by the Institutional Review Board.