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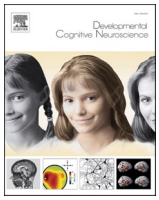

Leveraging big data to map neurodevelopmental trajectories in pediatric anxiety

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ABSTRACT

Anxiety disorders are the most prevalent psychiatric condition among youth, with symptoms commonly emerging prior to or during adolescence. Delineating neurodevelopmental trajectories associated with anxiety disorders is important for understanding the pathophysiology of pediatric anxiety and for early risk identification. While a growing literature has yielded valuable insights into the nature of brain structure and function in pediatric anxiety, progress has been limited by inconsistent findings and challenges common to neuroimaging research. In this review, we first discuss these challenges and the promise of 'big data' to map neurodevelopmental trajectories in pediatric anxiety. Next, we review evidence of age-related differences in neural structure and function among anxious youth, with a focus on anxiety-relevant processes such as threat and safety learning. We then highlight large-scale cross-sectional and longitudinal studies that assess anxiety and are well positioned to inform our understanding of neurodevelopment in pediatric anxiety. Finally, we detail relevant challenges of 'big data' and propose future directions through which large publicly available datasets can advance knowledge of deviations from normative brain development in anxiety. Leveraging 'big data' will be essential for continued progress in understanding the neurobiology of pediatric anxiety, with implications for identifying markers of risk and novel treatment targets.

1. Introduction

Anxiety disorders are common among youth, affecting approximately 30% of children and adolescents (Costello et al., 2005; Merikangas et al., 2010). The majority of anxiety disorders emerge during childhood and adolescence, with a median age of onset of 11 (Kessler et al., 2005). Nearly 50% of adolescents with anxiety disorders experience continued psychopathology in adulthood (Gregory et al., 2007), highlighting the significant risk for chronic mental health problems and the need for effective treatments early in life. In order to understand this period of risk, it is important to consider the substantial changes in structural and functional brain maturation that occur during development. Delineating how variation in these neurodevelopmental trajectories is associated with risk for anxiety disorders is critical for improving risk detection and identifying novel targets for treatments in youth. Human neuroimaging research has proved an invaluable resource for furthering our understanding of neural mechanisms underlying pediatric anxiety; however, key methodological challenges and inconsistent findings have hindered progress in this area. In this review, we describe existing studies that have used large cross-sectional and longitudinal neuroimaging datasets to inform knowledge about pediatric anxiety and demonstrate how such approaches can be leveraged to understand trajectories of risk. Further, we highlight promising directions for future research that capitalize on growing trends in reproducible methods to delineate neurodevelopmental mechanisms related to anxiety.

2. Age-related neural changes and pediatric anxiety

Human neuroimaging research has yielded important insights into neural mechanisms related to pediatric anxiety. Anxiety disorders are associated with alterations in the frontolimbic circuitry (e.g., ventromedial prefrontal cortex (vmPFC), amygdala, and hippocampus) (Gee and Casey, 2017) that governs fear learning, as well as large-scale networks such as the salience network and default mode network, which are respectively involved in responding to salient stimuli and self-referential processing (Strawn et al., 2020). Childhood and adolescence are marked by ongoing structural (Gee et al., 2016; Swartz et al.,

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2014) and functional (Calabro et al., 2019; Gabard-Durnam et al., 2014; Gee et al., 2013; Hare et al., 2008; Jalbrzikowski et al., 2017) changes in frontolimbic circuitry and large-scale functional networks. In particular, the development of prefrontal regions is more protracted than that of subcortical structures (Casey et al., 2019; Gogtay et al., 2004; Lenroot and Giedd, 2006), and structural (i.e., uncinate fasciculus) (Gee et al., 2016; Swartz et al., 2014) and functional (Calabro et al., 2019; Gabard-Durnam et al., 2014) connectivity of medial prefrontal regions with the amygdala and hippocampus continues to develop into young adulthood. Thus, mapping neurodevelopmental trajectories is important for understanding the etiology of anxiety and to relate neural changes to the emergence of symptomology.

2.1. Structural diagnostic differences

Previous neuroimaging research on anxiety disorders has identified several key structural alterations in frontolimbic circuitry, including the amygdala, vmPFC, anterior cingulate cortex (ACC), and insula (Gee and Casey, 2017). While the majority of existing research on anxiety-related structural differences has been conducted in adults, emerging studies in youth suggest similar patterns (Strawn et al., 2020). Several studies have identified structural abnormalities of the amygdala in youth with anxiety, but the direction of these alterations is inconsistent (Cohodes and Gee, 2017). Whereas some studies have found evidence for larger amygdala volumes in youth with anxiety disorders (e.g., De Bellis et al., 2000; Qin et al., 2014; Schienle et al., 2011), others have found reduced amygdala volumes in anxious youth (e.g., Milham et al., 2005; Mueller et al., 2013; Strawn et al., 2015). Previous studies have also demonstrated structural differences in regions of the prefrontal cortex (PFC) in pediatric anxiety disorders. For example, previous studies identified increased cortical thickness in the vmPFC and decreased gray matter volumes in the ventrolateral PFC in youth with anxiety disorders compared to non-anxious youth (Gold et al., 2017; Strawn et al., 2015). While prior research suggests anxiety-related increases in gray matter volume in the dorsal ACC, other studies have failed to identify differences in ACC volume between anxious and non-anxious youth (Mueller et al., 2013; Strawn et al., 2015). Finally, the existing literature suggests increased insula volume in youth with anxiety disorders compared to non-anxious youth (Mueller et al., 2013). Taken together, these findings suggest the presence of frontolimbic structural changes in pediatric anxiety, although the lingering inconsistencies among studies demonstrate the need for further work in this area.

2.2. Functional diagnostic differences

Consistent with evidence of altered structure in frontolimbic circuitry in pediatric anxiety, existing studies have demonstrated that youth with anxiety disorders display differences in neural function associated with core processes implicated in anxiety. Broadly, youth with anxiety show alterations in activation and functional connectivity of regions including the amygdala, hippocampus, and various subregions of PFC when reacting to or regulating reactivity to emotional stimuli, particularly those associated with threat, or when engaging in learning about salient stimuli in the environment. Relative to their non-anxious peers, youth with anxiety disorders display heightened activation of the amygdala, ACC, and ventral PFC when viewing fearful faces (Blair et al., 2011; McClure et al., 2007; Monk et al., 2008; Prater et al., 2013; Thomas et al., 2001) and angry faces (Blair et al., 2011; Monk et al., 2008). Additionally, compared to non-anxious peers, youth with anxiety disorders show alterations in connectivity between the medial (Kim et al., 2011), dorsolateral (Prater et al., 2013), and ventrolateral (Monk et al., 2008) PFC and amygdala in response to emotional stimuli, potentially reflecting weakened prefrontal control of amygdala reactivity. These differences in activation and connectivity may contribute to anxious children's tendency to show greater intensity of negative emotion (Carthy et al., 2010a, 2010b) and to interpret stimuli as more negative or threatening, relative to their non-anxious peers (Suveg and Zeman, 2004). Difficulty discriminating between threat and safety is another hallmark of anxiety disorders that is observed at the neural level (Britton et al., 2011; Duits et al., 2015; Graham and Milad, 2011; Jovanovic et al., 2014). During threat conditioning, adolescents with anxiety disorders display lower medial PFC activation than non-anxious adolescents, regardless of age (Haddad et al., 2015). In addition, anxious youth and adults exhibit lower subgenual ACC activation when engaged in threat appraisal during extinction recall compared to their non-anxious peers (Britton et al., 2013a). Finally, trait anxiety in youth may be associated with increased neural pattern similarity in prefrontal regions (e.g., vmPFC) between threat and safety during extinction recall (Glenn et al., 2020). Together, these findings suggest that neural discrimination between threat and safety is less pronounced and that specific prefrontal subregions may be recruited less during threat and safety learning among anxious individuals compared to their non-anxious peers.

Given evidence of alterations in attentional bias to threat in anxiety disorders (Roy et al., 2015), neuroimaging studies in youth with anxiety disorders have also focused on this process. Aberrant functional connectivity of the amygdala with the insula (White et al., 2017) and the ventrolateral PFC (Monk et al., 2008), as well as weaker connectivity between the rostrodorsal ACC and hippocampus/parahippocampus (Price et al., 2014), have been observed in anxious youth during tasks of attentional threat bias. Disruptions in the functional connectivity of amygdala-based networks are also present at rest for youth with anxiety (Roy et al., 2013). Positive associations between functional connectivity at rest and during an attentional bias task suggest that these profiles of functional connectivity are stable across conditions and present even in the absence of threatening information (Harrewijn et al., 2020). Anxious children also show alterations in inhibitory control, which may contribute to less effective control of attention (Cardinale et al., 2019; Ladouceur et al., 2009; Lonigan and Vasey, 2009; Susa et al., 2012). Reduced activation in the rostral ACC has emerged as a potential neural correlate of weaker inhibitory control in anxious youth (Swartz et al., 2014). Although these findings provide some insight into the neural mechanisms that may underlie behavioral and cognitive alterations in pediatric anxiety, much remains unknown about how these processes develop over time and whether neurodevelopmental trajectories differ in youth with anxiety disorders.

2.3. Age-related diagnostic differences

While most studies have not examined age-related diagnostic differences, some evidence suggests that anxiety-related changes in frontoamygdala circuitry may be age-dependent. In typical development, children display positive functional connectivity between the medial PFC and amygdala in response to emotional faces, and this pattern shifts to negative connectivity around the transition to adolescence (Gabard-Durnam et al., 2014; Gee et al., 2013; Jalbrzikowski et al., 2017). By contrast, youth with anxiety disorders show an opposite age-related pattern of medial PFC-amygdala functional connectivity in response to emotional faces, with increasing positive connectivity in adolescence (Kujawa et al., 2016). These findings highlight the importance of examining diagnostic differences through a developmental lens and are consistent with broader evidence of age-related discontinuities in pediatric anxiety disorders.

Examination of neural mechanisms relating to specific psychological processes during extinction recall shows that vmPFC engagement during threat appraisal, but not explicit threat memory, differs between anxious and non-anxious individuals in an age-dependent manner (Britton et al., 2013a; Gold et al., 2020). Specifically, anxious youth, but not non-anxious youth or anxious adults, exhibit elevated vmPFC activation when ambiguity between threat and safety is minimized during threat appraisal (Britton et al., 2013a). Thus, age discontinuities in anxiety disorders may occur based on the biological state of specific neural

circuits and the psychological processes in which they are engaged (Gee and Kribakaran, 2020; Gold et al., 2020). Though longitudinal research on pediatric anxiety has been limited thus far, one longitudinal study found that changes beginning in adolescence in the functional neural architecture supporting inhibitory control and motivation were associated with differing levels of anxiety in middle adulthood (Petrican and Grady, 2019). Future longitudinal work will be important for understanding how alterations in neural circuitry related to processes such as inhibitory control and safety learning may confer risk for anxiety.

As anxiety disorders commonly emerge during childhood or adolescence (Kessler et al., 2005), understanding clinical trajectories of anxiety is key to a developmental conceptualization of anxiety pathology. Evidence to date demonstrates some heterogeneity in the trajectories of anxiety depending on subtype. For example, separation anxiety disorder tends to emerge earlier in childhood, whereas social anxiety disorder tends to emerge later in childhood or during adolescence, and panic disorder and generalized anxiety disorder (GAD) may not emerge until even later in adolescence or early adulthood (Beesdo et al., 2009). As anxiety disorders are highly comorbid, building models that account for individual differences across comprehensive domains of functioning (e.g., behavioral, cognitive, social, etc.) and overlapping symptomology with other psychopathologies may be key for decoding individual risk throughout the lifespan. To this end, a longitudinal study of anxiety symptomology measured by the Screen for Child Anxiety Related Emotional Disorders (SCARED) across a 5-year period revealed substantial individual variability in the emergence of different subtypes of anxiety disorders as a function of age and sex (Hale et al., 2008). Delineating neurobiological trajectories associated with anxiety may provide important insight into the individual differences observed in trajectories of symptomatology.

3. Current challenges and the promise of big data

Though the extant literature has provided important insights into neural changes associated with pediatric anxiety, neuroimaging research, particularly with clinical developmental samples, comes with many challenges. Collection of magnetic resonance imaging (MRI) data is costly and time-consuming, often resulting in relatively small sample sizes with low statistical power (on average between 8–31% in published neuroscience studies) (Button et al., 2013). Such low statistical power both decreases the probability of detecting a true effect and increases the probability of a statistically significant result that does not reflect a true effect (Button et al., 2013). Obtaining robust sample sizes can be particularly difficult when recruiting clinical and developmental populations, and studies of pediatric anxiety may be particularly susceptible to attrition (e.g., Gee and Kribakaran, 2020; Gold et al., 2020; Shechner et al., 2014). Due to their anxiety, children with anxiety disorders may be less likely to begin or complete functional MRI (fMRI) studies, which involve a novel environment and require lying very still in a loud, tight space. Moreover, the nature of some tasks used to assess threat learning or attention to threat, which are particularly relevant to anxiety, can be aversive by definition and thus more associated with attrition. Given that children with the highest anxiety severity are most likely to drop out of such studies, the range of anxiety represented in pediatric neuroimaging studies is likely to be restricted. This restricted range of anxiety further lowers statistical power and is important to consider when interpreting findings or attempting to generalize findings to clinical populations.

Reproducible results are important to ensure accuracy and external validity of research findings. Likely due to a combination of factors including low statistical power and differences in analytic approaches, many existing findings in neuroscience, particularly results from fMRI studies, fail to replicate in independent datasets (Button et al., 2013; Poldrack et al., 2017). The substantial flexibility available in neuroimaging data analysis can introduce additional experimental degrees of freedom and impede valid, reproducible results (Poldrack et al., 2017). In a striking recent example of this, when 70 independent research teams were given the same fMRI dataset to test pre-defined hypotheses, no two teams selected the same workflows nor generated identical conclusions (Botvinik-Nezer et al., 2020). Inconsistent results limit interpretability and generalizability about the true relationship between neural measures and behavior or clinical symptoms. As in the broader neuroimaging literature, there have been inconsistent findings related to brain structure and function in youth with anxiety disorders. Although diagnostic differences have often been observed in the domains of structural and functional neuroimaging, the directionality and consistency of alterations related to pediatric anxiety are unclear. These inconsistent findings reflect substantial limitations of neuroimaging research as it has traditionally been employed and underscore the need to adopt approaches that will enhance reproducibility.

The use of large, collaborative datasets can help to circumvent many of these challenges and offers exciting promise for advancing our understanding of neurodevelopmental trajectories associated with pediatric anxiety. So-called ‘big data’ studies have emerged in parallel across many scientific fields and are characterized as cohesive large samples of homogenous measures. The designation of a dataset as “large” is relative between fields; in the field of genetics, for example, the UK Biobank has collected a sample of half a million participants (Allen et al., 2012) and in the field of economics some datasets of consumer behavior have billions of data points (Fosso Wamba et al., 2015). By contrast, sample sizes in human neuroimaging are often on the order of tens of participants (Poldrack et al., 2017), in part because these data are costly to collect both in terms of time and resources. Thus, in the context of human neuroscience research, datasets with several hundreds or thousands of participants are orders of magnitude larger than traditional studies and represent a marked increase in statistical power available to researchers. Further, these large datasets have increasingly employed neuroimaging (Biswal et al., 2010) in addition to broader measures of behavior. Many of these datasets follow open science models and are publicly available to members of the research community. Importantly, these studies have allowed many researchers access to shared rich multimodal data in large cohorts. Along with facilitating access and broader use of collected data, these studies have increased statistical power and provided new opportunities to enhance methodological rigor and reproducibility (Glasser et al., 2016). Multi-site data collection with identical protocols across sites has proved feasible and emerged as a core strategy for generating these large datasets, leading to a cohesive dataset much larger than a typical individual lab could feasibly collect (Jernigan et al., 2016; Volkow et al., 2018). Larger datasets will be essential to advancing knowledge in this area as meta-analyses have revealed that tasks relevant to studying anxiety often have small to medium effect sizes, requiring sample sizes larger than current norms in the field to be adequately powered (Fig. 1). Moreover, large, multi-site studies provide opportunities to assess more comprehensive models of behavioral and clinical phenomena through consistent measurement of potential explanatory variables.

4. Examining neurodevelopment and pediatric anxiety in big data studies

Given challenges inherent to neuroimaging research, particularly with clinical developmental samples, big data studies will be essential to continued progress in identifying neurodevelopmental trajectories associated with pediatric anxiety. A growing number of large cross-sectional or longitudinal neuroimaging studies of childhood and/or adolescence are available with measures related to anxiety (Alexander et al., 2017; Casey et al., 2018; Evans, 2006; Hubbard et al., 2020; Jaddoe et al., 2006; Jernigan et al., 2016; Nooner et al., 2012; Pausova et al., 2017; Satterthwaite et al., 2016; Salum et al., 2015; Schumann et al., 2010; Somerville et al., 2018; Volkow et al., 2018). Each of these datasets contains measures of structural and/or functional neuroimaging, anxiety symptoms, and various other relevant measures in

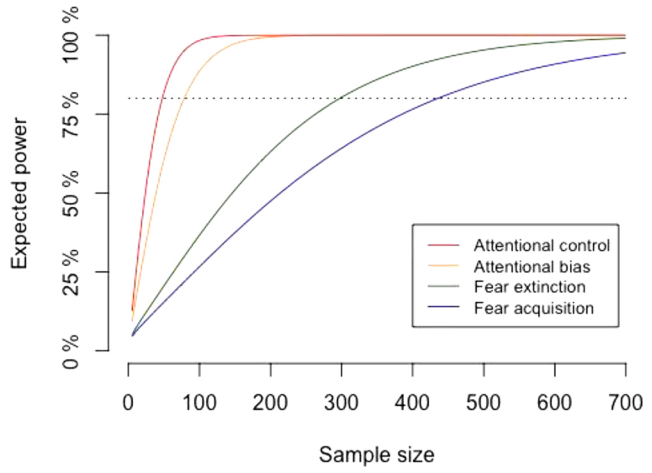

Fig. 1. Sample size needed for adequate statistical power for tasks relevant to the study of anxiety. These power curves represent sample sizes needed for an adequately powered two-sample *t*-test for an alpha value of 0.05. The dotted horizontal line marks 80% statistical power. Effect sizes observed in anxious populations for tasks of attentional bias (d = 0.45, Bar-Haim et al., 2007), fear acquisition (d = 0.19, Lissek et al., 2005), fear extinction (d = 0.23, Lissek et al., 2005), and attentional control (d = 0.58, Shi et al., 2019) were determined based on meta-analyses.

cognitive, emotional, social, behavioral, physical, and genetic domains (Table 1). The breadth of domains captured in many big data studies provides unique opportunities to examine a rich landscape of potential mediators and moderators that may provide unique mechanistic insights and elucidate interactions with key environmental (e.g., stress) or developmental (e.g., puberty) factors. The construction of more complex models that may better explain variance across individuals could help to reconcile inconsistent findings in the current literature on pediatric anxiety. Further, anxiety varies continuously from normative to pathological levels, and dimensional approaches to modeling anxiety can enhance statistical power. The highly dimensional symptom data that are sometimes collected in large datasets are important for examining continuous variation in brain structure or function associated with differential levels of anxiety severity, rather than relying on categorical diagnostic differences. Moreover, such dimensional data in combination with diagnostic information could be used to test whether there are more discrete shifts in brain structure or function that correspond to a clinical threshold. Another advantage of big data studies is the opportunity to test for replication or generalizability of findings. Many of these datasets have been designed to collect overlapping measures for key constructs. As examples, several studies outlined in Table 1 collect the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997) diagnostic interview to assess psychopathology, the NIH Toolbox (Gershon et al., 2010) to assess neurocognitive and behavioral functioning, and the PhenX Toolkit (Hamilton et al., 2011) to assess a wide array of phenotypic domains. These congruent measures allow for ease of facilitating comparisons across studies and testing for generalizability (e.g., Schork et al., 2019). In addition, assessment across multiple symptom domains (e.g., Barch et al., 2018) facilitates testing whether findings are specific to anxiety or common across other symptom domains, as anxiety is highly comorbid. Such models spanning multiple symptom domains may be key to disentangling neural markers that are specific to individual anxiety disorders versus markers that are common across diagnoses. As anxiety disorders are highly comorbid (Kessler et al., 2005) and are commonly characterized by physiological arousal, avoidance, and feelings of disproportionate worry and distress, it is plausible that shared neural bases could underlie many anxiety diagnoses. On the other hand, the phenotypic signatures of specific anxiety disorders can be quite heterogeneous (e.g., the typical presentation of a specific phobia is quite different from that of generalized anxiety disorder), so some specificity in neural bases is also conceivable, which could be identified with the highly dimensional models based on big data. Meta-analytical consortia, such as the Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA)-Anxiety Working Group, which has pooled many individual datasets of generalized anxiety disorder, social anxiety disorder, specific phobia, and panic disorder subgroups into the largest neuroimaging dataset to date focused on anxiety (Bas-Hoogendam et al., 2020), may be especially valuable for investigations to this end.

4.1. *Complementary strengths of large datasets*

Given different study designs and data modalities, existing big data studies have complementary strengths and are poised to address distinct questions related to pediatric anxiety (for open questions well-suited to investigation with large datasets, see Table 2). For example, the Boston Adolescent Neuroimaging of Depression and Anxiety (BANDA) study, which is harmonized with the Human Connectome Project (HCP), has a uniquely large clinical sample with a focus on recruiting adolescents ages 14–17 (N = 225) with and without anxiety and depression (Hubbard et al., 2020). The fMRI tasks in the BANDA study focus on processes with direct clinical relevance to anxiety (e.g., emotion processing, emotional interference), making it an ideal dataset for probing brain function in clinically anxious youth and parsing heterogeneity in anxious subtypes. In addition, given the focus on anxiety and depression, the BANDA study will be well positioned to dissociate neural processes that are uniquely altered in anxiety from those that have transdiagnostic relevance for internalizing disorders. Other large cohort studies are well positioned to examine genetic factors and heritability related to anxiety. The longitudinal Adolescent Brain Cognitive Development (ABCD) Study includes a twin substudy of 800 pairs of same-sex twins across four sites. This design will allow for comparisons within and between monozygotic and dizygotic twin pairs to examine genetic and environmental contributions to associations between neurodevelopment and anxiety (Iacono et al., 2018). The Saguenay Youth Study (SYS) contains multimodal data from adolescent siblings and their parents from a region of Québec with a large genetic founder-effect, characterized by low genetic diversity caused by a small number of individuals founding the population of an isolated area (Braekeleer, 1991; Pausova et al., 2017). The reduced genomic heterogeneity in this sample makes this dataset well-suited for researchers interested in studying complex traits associated with predisposition toward anxiety and its heritability. The Healthy Brain Network (HBN) biobank collected by the Child Mind Institute aims to collect a community sample of 10,000 youths ages 5–21 from the New York City area (Alexander et al., 2017). This dataset has a unique suite of measures including genetic information, blood and urine biosamples, and strength and cardiovascular physical fitness measures, which will allow researchers to examine biophysical interactions as they relate to risk for anxiety.

Such large cross-sectional and longitudinal studies will be essential to mapping neurodevelopmental trajectories that are associated with anxiety. One promising strategy to advance knowledge in this domain is to leverage these big data studies to test and expand upon existing hypotheses and age-related results derived from smaller cross-sectional studies of pediatric anxiety. In addition, results that have emerged from large cross-sectional datasets can be tested in longitudinal datasets that allow for the examination of within-subject trajectories, especially in studies with cohorts overlapping in age. Critically, large datasets with broad age ranges or longitudinal follow-up timepoints can be used to address questions about structural and functional neural factors that characterize the onset, progression, and remission of anxiety in youth. Cohesive large datasets additionally present strengths complementary to those of individual studies or meta-analyses that pool findings across smaller individual studies. The utility of meta-analytical results hinges upon the quality of the constituent studies. When a meta-analysis is based upon under-powered studies, as discussed above, findings may be

Table 1
Representative large developmental datasets that include magnetic resonance imaging data. Additional multimodal measures collected in each dataset are displayed. Key: Int. = clinical interview (e.g., K-SADS); MH = self- or parent-reported mental health questionnaires (e.g., BDI, SCARED); Struc. = structural MRI (e.g., T1w, proton density); rsMRI = resting state MRI; dMRI = diffusion MRI (e.g., DTI, HARDI); fMRI = functional MRI (e.g., BOLD signal measured during task); Beh. = behavioral measures; Bio. = biological samples; Cog. = cognitive measures; Emo. = emotional measures (e.g., Youth Self Report); Gen. = genetic samples; L/E = lifestyle or experiential measures; Phys. = physical or medical measures; Soc. = social measures; Sub. = substance use measures.

Dataset	Location(s)	Collected sample size (N)	Longitudinal or cross-sectional	Ages of partic-ipants	Clinical measures		Neuroimaging measures				Additional measures								
					Int.	MH	Struc.	rsMRI	dMRI	fMRI	Beh.	Bio.	Cog.	Emo.	Gen.	L/E	Phys.	Soc.	Sub.
Adolescent Brain Cognitive Development Study (ABCD)	21 sites across US	11,878	Longitudinal	9–20	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Boston Adolescent Neuroimaging of Depression and Anxiety (BANDA)	Greater Boston, MA area	245	Both	14–17	X	X	X	X	X	X	X		X	X		X	X		X
Brazilian High Risk Cohort Study (BHRC)	Porto Alegre and São Paulo, Brazil	2,511	Longitudinal	6–21	X	X	X	X	X		X	X	X	X	X	X		X	X
Child Mind Institute Healthy Brain Network (HBN)	Greater New York City, NY area	2,092	Cross-sectional	5–21	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
The Generation R study	Greater Rotterdam, Netherlands area	9,749	Longitudinal	0–16	X	X	X	X	X		X	X	X	X	X	X	X	X	
IMAGEN study	8 sites across Western Europe	2,000	Longitudinal	14–22	X		X	X	X	X	X		X	X	X	X			X
Lifespan Human Connectome Project in Development (HCP-D)	5 sites across US	1,344	Both	5–21	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nathan Kline Institute-Rockland Enhanced Sample (NKI-RS)	Greater New York City, NY area	1,495	Both	6–85	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NIH MRI Study of Normal Brain Development	6 sites across US	556	Longitudinal	0–18	X	X	X		X		X	X	X	X			X		
Pediatric Imaging, Neurocognition, and Genetics (PING)	10 sites across US	1,493	Cross-sectional	3–20		X	X	X	X		X		X	X	X	X	X	X	X
Philadelphia Neurodevelopmental Cohort (PNC)	Greater Philadelphia, PA area	9,267	Cross-sectional	8–21	X	X	X	X	X	X	X		X	X	X	X	X		X
Saguenay Youth Study (SYS)	Saguenay Lac Saint-Jean region of Québec, Canada	1,029	Cross-sectional	12–18	X	X	X				X	X	X	X	X	X	X	X	X

Table 2
Prior pediatric anxiety research findings and remaining open questions that are well suited for investigation with big data.

Domain	Prior research	Open questions
Structural alterations	• Reduced cortical thickness in GAD (Newman et al., 2016) • No cortical thickness differences observed in sample of any anxiety disorder (Merz et al., 2018a) • Greater amygdala volumes in anxious youth (De Bellis et al., 2000; Qin et al., 2014; Schienle et al., 2011) • Reduced amygdala volumes in anxious youth (Milham et al., 2005; Mueller et al., 2013; Strawn et al., 2015) • vmPFC engagement during threat appraisal differs between anxious and non-anxious youth in an age-dependent manner (Britton et al., 2013a; Gold et al., 2020)	• How do differences in brain structure vary based upon anxiety subtype during childhood and adolescence? To what extent are these neural markers common across anxiety disorders or distinct as a function of diagnosis? • Are volumetric differences in the amygdala present in anxious youth? To what extent do these volumetric differences relate to function? • To what extent can trajectories of neurodevelopment accurately predict onset of anxiety? Are certain anxiety diagnoses better able to be predicted from neural bases? • How do age-related alterations in neural circuitry related to processes relevant to anxiety, such as threat learning, interact with the emergence of pediatric anxiety?
Functional alterations	• Anxious youth show altered functional connectivity between the amygdala and the medial (Kim et al., 2011), dorsolateral (Prater et al., 2013), and ventrolateral (Monk et al., 2008) prefrontal cortex in response to emotional stimuli • Anxious youth show aberrant functional connectivity between the amygdala and insula (White et al., 2017), amygdala and ventrolateral prefrontal cortex (Monk et al., 2008), and rostrodorsal ACC and hippocampus/parahippocampus (Price et al., 2014) during attentional threat bias tasks • Age discontinuities in anxiety disorders may occur based on the biological state of specific neural circuits and the psychological processes in which they are engaged (Gold et al., 2020)	• Are alterations in connectivity between the amygdala and prefrontal regions causally related to anxiety symptomatology or hypervigilance to negative emotion? • How does aberrant connectivity between these regions mechanistically support attentional bias to threat? • How do neural markers of anxiety derived from task and resting-state fMRI data relate to one another, and how might this change across development? • To what extent do neural correlates and mechanisms related to anxiety remain consistent or shift across development?

skewed and prone to some of the same limitations as smaller individual studies. In addition, meta-analytical approaches of a given construct of interest often rely on studies with substantial variability in measures, exclusion criteria, or acquisition parameters, which can increase noise. On the other hand, consistent results from multiple studies using different measures for the same construct support the external validity and generalizability of the findings. Big datasets can ensure harmonization of study design across sites and enhance statistical power. However, there are clear trade-offs. Particularly when it comes to clinical developmental neuroscience, large-scale efforts may not have the flexibility to collect in-depth clinical batteries or to focus on patient populations to the same extent as smaller-scale, investigator-led studies. Thus, a balance of big data studies and meta-analyses of smaller individual studies will be important to continue to advance the field.

4.2. Delineating age-related changes in large datasets

Various large-scale cross-sectional studies allow for the examination of age-related neural patterns related to anxiety across a broad age range. Examples include multi-site studies such as the Lifespan Human Connectome Project Development (HPC-D) study (N > 1,300, ages 5−21, 5 sites; Somerville et al., 2018), which has data across imaging modalities, and the Pediatric Imaging, Neurocognition, and Genetics (PING) study (N > 1400, ages 3−20, 10 sites; Jernigan et al., 2016), which includes structural, diffusion-weighted, and resting-state MRI. These studies are also well-suited for investigating premorbid or early correlates of anxiety, as they begin sampling in early childhood and the median age of onset for anxiety disorders onset is 11 (Kessler et al., 2005). While large-scale longitudinal studies are less common, there are also a number of longitudinal studies with measures of anxiety. The ABCD Study represents the largest longitudinal study of neurodevelopment and contains measures of structural, diffusion-weighted, functional, and resting-state MRI (Casey et al., 2018). The large size (N > 11,000; 21 sites) of the ABCD Study and its long-term longitudinal follow-up across the second decade of life (Volkow et al., 2018) will be particularly valuable for mapping trajectories and examining temporal relationships between neural measures, anxiety, and variables across a broad range of other domains including cognition, physical health, culture, and environment. The longitudinal Generation R study conducted in the Netherlands (N > 9000) is particularly notable for its broad age range (birth-16 years of age), with some measures available as early as prenatally (Jaddoe et al., 2006). For later development, the IMAGEN study (N > 2,000; 8 sites) provides a range of imaging measures across ages 14−22 (Schumann et al., 2010). Though evidence suggests that adult templates of normalized brain space are largely acceptable for examining pediatric change (Burgund et al., 2002), investigators may wish to consider using graded age-specific brain templates for a more fine-grained examination of neurodevelopmental trajectories (e.g., Sanchez et al., 2012 for open-source templates spanning 4.5–19.5 years of age in 6-month intervals). Taken together, these big data studies provide many opportunities to examine neurodevelopmental trajectories associated with anxiety.

4.3. Existing knowledge about anxiety-related trajectories from large datasets

Big data studies have already begun to facilitate such contributions. In the structural domain, examination of cortical surface area and thickness in the PING dataset showed that higher levels of anxiety, specifically symptoms of generalized anxiety disorder, are associated with reduced global cortical thickness and lower cortical surface area of the vmPFC (Newman et al., 2016). Another study using the PING dataset did not find associations between anxiety symptoms and cortical thickness, surface area, or gray matter volume (Merz et al., 2018a). Notably, whereas Newman and colleagues specifically examined generalized anxiety, Merz et al. examined a sample characterized by any type of anxiety, suggesting that differences in brain structure associated with anxiety may differ based on subtype. Large datasets will be important for helping researchers to continue to map age-related structural changes associated with anxiety and to disentangle associations between brain development and various dimensions of anxiety. In the functional domain, data from 1,129 youth in the Philadelphia Neurodevelopmental Cohort (PNC) have shown that some functional activation patterns during working memory, probed using a fractal n-back task, are associated with overall psychopathology, whereas anxiety symptoms in particular are associated with increased activation in the executive network (Shanmugan et al., 2016). These findings suggest that neural correlates of working memory, although often altered in many psychiatric conditions, exhibit some unique changes in pediatric anxiety. Extending this work, future research using large developmental cohorts should investigate functional trajectories associated with specific aspects of executive functioning that have been

strongly associated with anxiety disorders, such as inhibitory control.

To this end, large longitudinal studies can additionally play a pivotal role in mapping developmental trajectories of neural function related to processes that are implicated in anxiety disorders, such as threat learning and emotional reactivity. In particular, they may help reconcile inconsistent findings in the extant literature related to potential neurodevelopmental differences in anxiety. For example, the longitudinal BANDA study is taking a big data approach to examine functional trajectories related to emotional reactivity, in addition to responsiveness to reward and cognitive control, and their associations with depression and anxiety symptomatology. The study employs tasks shown, through smaller studies, to elicit process-specific neural changes linked to anxiety and depression. Specifically, the BANDA study uses the Emotion Processing Task (EPT) to examine emotional reactivity, the Incentive Processing Task to probe responsiveness to reward, and the Emotion Interference Task to investigate cognitive control. From this research, longitudinal functional imaging data from the EPT, for example, can be used to test whether functional patterns of activation during emotional reactivity differentially predict changes in anxiety versus depressive symptomatology later in adolescence (Hubbard et al., 2020). Taken together, these examples indicate some of the ways that large datasets can be used to delineate process-specific neurodevelopmental trajectories specific to and predictive of anxiety disorders.

4.4. Mapping risk for anxiety with large datasets

Large-scale longitudinal studies, in particular, have an essential role in examining specific risk factors that have been closely linked with the development of anxiety disorders. It is particularly important to study risk factors over time in order to examine potential pathways to the development of anxiety disorders. Both large-scale, multi-site studies as well as more circumscribed investigator-led studies offer great potential for investigating potential links between risk factors, such as early temperament, and neurodevelopment associated with future anxiety diagnoses. Behavioral inhibition (BI), is a temperamental trait characterized by hypervigilance to threat and novelty, which has been associated with increased risk for anxiety disorders (Liu and Pérez-Edgar, 2019; Pérez-Edgar and Guyer, 2014). The Temperament Over Time Study first screened children at four months of age and has continued to follow children selected for high reactivity to novel stimuli, as well as an unselected control group, across development (Hane et al., 2008). Through such longitudinal studies, BI has been associated with alterations in frontolimbic function such as greater dorsolateral PFC activation in children directing attention away from threat (Fu et al., 2017) and greater amygdala activation in adolescents attending to subjective fear (Pérez-Edgar et al., 2007). Longitudinal neuroimaging of neonates revealed that functional connectivity profiles in default mode and ventral attention networks are associated with BI in toddlers (Sylvester et al., 2018a), highlighting the feasibility of examining neural processes associated with risk for anxiety very early in life. Characterizing trajectories of BI and related traits such as shyness (Sylvester et al., 2018b) in big datasets will be particularly helpful for assessing continuous variation (i.e., across a broad range from normative to extreme levels) in risk factors for anxiety. Sex differences may also confer variability in risk for anxiety disorders, as evidence from the PNC dataset suggests that elevated perfusion in the amygdala during adolescence mediates higher trait anxiety in postpubertal female participants relative to male participants (Kaczkurkin et al., 2016).

Furthermore, studies employing large shared datasets have already made several contributions to identifying potential etiological influences, such as genetic factors or environmental exposures, that may increase risk for anxiety at specific developmental stages. Paralleling cross-species evidence in rodents, data from the PING study showed that the impact of genetic variation related to endocannabinoid signaling on frontolimbic structural connectivity and anxiety emerges during adolescence (Gee et al., 2016). Also in the PING study, Newman et al. found that associations between symptoms of generalized anxiety and reduced cortical thickness/surface area are stronger in childhood and early adolescence than in late adolescence or young adulthood (Newman et al., 2016). In the domain of environmental factors, another study utilizing the PING dataset showed that an association between lower family income and parental education with smaller amygdala volume is specific to adolescence, and not observed in childhood, and that lower parental education is associated with higher levels of anxiety and depression (Merz et al., 2018b). These age-specific structural findings underscore the need to conceptualize risk factors for anxiety in the context of trajectories, rather than as static elements, since some factors are associated with greater risk only at certain developmental stages. Furthermore, longitudinal neural evidence from the IMAGEN study has demonstrated that changes in putamen and caudate volumes during adolescence mediate the association between peer victimization and anxiety (Quinlan et al., 2018). These findings highlight deviations from normative brain development that are associated with potential risk factors for anxiety across a variety of domains and help to inform a more complete picture of how anxiety emerges.

5. Limitations and future directions

Though large datasets offer many advantages, important challenges remain (for a concise summary of advantages and disadvantages, please see Table 3). First, test-retest reliability of fMRI has been identified as a central concern and is poorer with longer durations between scans (Herting et al., 2018), making it difficult to isolate true developmental change in longitudinal studies that typically collect scans months or years apart. Selecting tasks with high behavioral reliability and validity, such as tasks of emotion processing (Gee et al., 2015; Haller et al., 2018), or tasks that are associated with reliable patterns of functional activation, such as attentional bias toward threat (Britton et al., 2013b; White et al., 2016), at the stage of experimental design may be particularly useful for imaging studies. In addition, longitudinal designs may help in assessing the voxel-wise reliability of task effects to isolate true developmental change from fluctuation in the blood-oxygen-level-dependent (BOLD) signal due to noise (e.g., Britton et al., 2013b; van den Bulk et al., 2013; White et al., 2016). Reporting individual task reliability to a common platform to facilitate selection of tasks that have higher reliability at the design stage has emerged as one proposed initiative to address this challenge (Herting et al., 2018). Second, the detection of very small effect sizes is more likely in large studies; however, these

Table 3
Key advantages and challenges of using big datasets to study pediatric anxiety.

Key advantages of 'big data' to study pediatric anxiety	Key limitations of 'big data' to study pediatric anxiety
• Sample sizes can be orders of magnitude larger than is feasible for individual labs to collect • Sample sizes are large enough to detect small effects for some anxiety-relevant tasks • Higher statistical power is available to detect true effects • There is opportunity to replicate findings from previous smaller studies and to adjudicate inconsistent findings from the literature • Overlapping measures between some large datasets allow for testing replication of results • Broad domains of collected measures allow for comprehensive dimensional modeling of risk • Open access structures of many datasets allow for greater utility of collected data and promote replicability	• Very small effects that can be detected by virtue of large sample sizes may not be clinically or biologically meaningful • Many datasets collect a community sample and may not include a sufficient number of individuals meeting diagnostic criteria for analyses that rely on diagnoses • Many big datasets are from a single geographic area, which may limit generalizability of findings • Large amounts of data require greater computational resources and skills

effects may not be biologically or clinically meaningful (Dick et al., 2020; Smith and Nichols, 2018). Reporting effect sizes and confidence intervals alongside significant p-values in publications will allow for greater context and care in interpreting results (Dick et al., 2020). Third, despite some studies with large sample sizes, the number of youth who meet criteria for an anxiety disorder in a representative community sample that is not specifically ascertained based on clinical criteria is still limited. However, multi-site studies have proven to be effective and necessary for studies of conditions that are less common (Cannon et al., 2008). Fourth, the storage and computational capacities needed to work efficiently with the volume of data captured in large datasets is by definition greater than resources typically required for individual lab studies. As such, additional funding may need to be allocated from departments or funding agencies to labs working with large datasets, specifically to support adequate storage, cluster computing cores, and computational training for personnel. Finally, capturing the breadth of measures obtained in many big data studies requires vast resources and researcher and participant time. Thus, it would be rare for a large-scale study to provide the depth of measures related to anxiety (e.g., clinical assessment, fMRI tasks) that is more typical of smaller-scale studies focused specifically on anxiety. As such, the nature of questions related to pediatric anxiety that can be addressed with traditional big data studies will be inherently somewhat circumscribed.

Collecting neuroimaging data in clinical samples with protocols harmonized to those of large-scale studies of typically developing youth or community samples is a promising approach to extend the clinical utility of big data. An example of this approach is the BANDA study, in which the sampling strategy ensures that a large proportion of the sample will have an anxiety disorder, the assessment battery provides additional depth to focus on anxiety, and the overall protocol is harmonized to the HCP-D study to facilitate comparison. Collaborations that pool data across smaller investigator-led studies may also help to bridge the gap between traditional big data and isolated studies. For example, while consortium-based collaborations may be ideally situated to capture general measures with robust samples, collaborations among a smaller group of investigators might be better positioned to probe more nuanced or exploratory measures related to anxiety and to study even more specialized populations, such as treatment-seeking anxious youth. Increased investment and attention to such research efforts can therefore address some of the challenges that accompany investigating neurodevelopmental trajectories associated with clinical phenomena in big data studies.

Ongoing research with big data will play a central role in delineating neurodevelopmental trajectories associated with anxiety, including by more rigorously testing hypotheses that have been generated in smaller-scale and cross-sectional studies, and by helping to resolve inconsistent findings. As longitudinal large datasets typically track symptom severity and clinical presentation in an observational manner, the knowledge gained can be best applied in a complementary fashion to smaller studies or clinical trials researching treatment as a primary independent variable. Moreover, this work ultimately has important clinical implications that include enhancing early identification of risk, identifying novel treatment targets, and informing efforts to optimize the efficacy of evidence-based treatments (Cohodes and Gee, 2017). Although current evidence-based treatments (namely cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRI)) can be highly effective treatments for pediatric anxiety, up to 50% of clinically anxious children and adolescents do not respond sufficiently to these interventions (Ginsburg et al., 2018; Walkup et al., 2008). Given dynamic changes in brain maturation, the mechanisms underlying anxiety and optimal approaches for intervention are likely to differ across development. However, current treatments for clinically anxious youth, such as CBT, have been based largely on principles studied in adults (Lee et al., 2014). Knowledge gleaned from big data studies regarding changes in frontolimbic circuitry and large-scale networks throughout childhood and adolescence could be leveraged to optimize interventions for pediatric anxiety disorders based on the biological state of the developing brain (Casey et al., 2015).

Furthermore, much remains unknown about how neural measures may predict the onset of anxiety disorders or treatment outcomes in youth. Existing studies have largely examined associations between neural measures at baseline and symptom reduction following treatment but have not tested prediction at the individual level or examined the extent to which neural measures are related to treatment outcomes over and above clinically observable phenomena. To have meaningful translational value, neural predictors must be tested in external samples and improve prediction relative to more readily obtained clinical and behavioral measures (Gabrieli et al., 2015). Evidence in adults suggests that neural measures may indeed enhance clinical prediction (Doehrmann et al., 2013), and future research in youth will be important to replicate existing findings in larger samples and test their generalizability. In addition to predicting response to a single treatment, future research that identifies neural markers that can improve differential prediction of how an individual may benefit from one treatment versus another (e.g., White et al., 2017) would be particularly useful for enhancing personalized medicine. International collaborations will be important for generalizable findings of global clinical relevance. The ENIGMA-Anxiety Database, a meta-analytical consortium containing many neuroimaging datasets from 16 countries across 5 continents (Bas-Hoogendam et al., 2020), is an excellent example of this approach on a global scale. Taken together, this burgeoning area of the field may play an important role in determining when and for whom different treatments for anxiety will be most effective, as well as informing novel approaches to optimize existing treatments based on mechanisms that will target specific stages of neurodevelopment.

6. Conclusions

Pediatric anxiety disorders place a major burden on public health. Given the early age of onset and chronic course when left unaddressed, there is a clear need to enhance early identification of risk for anxiety disorders in youth. Delineating neurodevelopmental trajectories associated with anxiety has the potential to increase understanding of risk at key times in childhood and adolescence. Large-scale cross-sectional and longitudinal studies can mitigate some of the limitations of smaller neuroimaging studies and increase the possibility of identifying robust and reproducible patterns of brain structure and function associated with anxiety symptomatology. In this review, we highlight early findings from big data studies that demonstrate how developmental neuroscience can employ best practices for reproducibility to identify neurodevelopmental trajectories associated with risk. Leveraging advances in neuroscience and collaborative research thus offers a promising pathway to addressing the immense burden of pediatric anxiety through a deeper understanding of trajectories of risk across development.

Data statement

To facilitate ease of access to researchers wishing to work with the datasets mentioned in the manuscript, links to descriptive papers for each dataset and links to the data repository (or instructions for accessing the data repository) for each dataset are provided.

Adolescent Brain Cognitive Development (ABCD) Study

Descriptive papers: Casey et al., 2018: https://doi.org/10.1016/j.dcn.2018.03.001 & Volkow et al., 2018: https://doi.org/10.1016/j.dcn.2017.10.002.

Data repository/Instructions for accessing: https://nda.nih.gov/abcd.

Boston Adolescent Neuroimaging of Depression and Anxiety (BANDA)

Descriptive paper: Hubbard et al., 2020: https://doi.org/10.1016/j.nicl.2020.102240.

Data repository/Instructions for accessing: data soon to be made available on https://nda.nih.gov/; present study website https://banda.mit.edu/.

Brazilian High Risk Cohort Study (BHRC)

Descriptive paper: Salum et al., 2015: https://doi.org/10.1002/mpr.1459.

Data repository/Instructions for accessing: https://osf.io/ktz5h.

Child Mind Institute Healthy Brain Network (HBN)

Descriptive paper: Alexander et al., 2017: https://doi.org/10.1038/sdata.2017.181.

Data repository/Instructions for accessing: http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/.

The Generation R Study

Descriptive paper: Jaddoe et al., 2006: https://doi.org/10.1007/s10654-006-9022-0.

Data repository/Instructions for accessing: https://generationr.nl/researchers/collaboration/.

IMAGEN Study

Descriptive paper: Schumann et al., 2010: https://doi.org/10.1038/mp.2010.4.

Data repository/Instructions for accessing: https://imagen-europe.com/resources/imagen-dataset/.

Lifespan Human Connectome Project in Development (HCP-D)

Descriptive paper: Somerville et al., 2018: https://doi.org/10.1016/j.neuroimage.2018.08.050.

Data repository/Instructions for accessing: https://www.humanconnectome.org/study/hcp-lifespan-development/data-releases.

Nathan Kline Institute-Rockland Enhanced Sample (NKI-RS)

Descriptive paper: Nooner et al., 2012: https://doi.org/10.3389/fnins.2012.00152.

Data repository/Instructions for accessing: http://fcon_1000.projects.nitrc.org/indi/enhanced/access.html.

NIH MRI Study of Normal Brain Development

Descriptive paper: Evans, 2006: https://doi.org/10.1016/j.neuroimage.2005.09.068.

Data repository/Instructions for accessing: http://pediatricmri.nih.gov.

Pediatric Imaging, Neurocognition, and Genetics (PING)

Descriptive paper: Jernigan et al., 2016: https://doi.org/10.1016/j.neuroimage.2015.04.057.

Data repository/Instructions for accessing: https://nda.nih.gov/edit_collection.html?id=2607.

Philadelphia Neurodevelopmental Cohort (PNC)

Descriptive paper: Satterthwaite et al., 2015: https://doi.org/10.1016/j.neuroimage.2015.03.056.

Data repository/Instructions for accessing: https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000607.v3.p2.

Saguenay Youth Study (SYS)

Descriptive paper: Pausova et al., 2017: https://doi.org/10.1093/ije/dyw023.

Data repository/Instructions for accessing: http://saguenay-youth-study.org/scientific-community/collaborative-interest/.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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