Review article

Adolescent brain development and depression: A case for the importance of connectivity of the anterior cingulate cortex

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ABSTRACT

We propose that structural and functional connectivity of the anterior cingulate cortex (ACC) represents a critical component of adolescent developmental psychopathology. We hypothesize that connectivity of the ACC, a hub for integrating cognitive, affective, and social information to guide self-regulation across domains, supports adaptive development of self-regulation during adolescence and that, conversely, disrupted maturation of ACC connectivity contributes to the development of depression. To integrate findings on typical development, we report results of a meta-analysis of diffusion imaging findings of typical adolescent development of the cingulum and anterior thalamic radiations, the tracts most relevant to ACC connectivity, and provide a critical review of the literature on ACC functional connectivity. Finally, we review the evidence for altered structural and functional connectivity in adolescents with depression. Although the evidence for our claim is persuasive, a more comprehensive understanding of the ACC's role depends upon future investigations with sophisticated modeling of networks, prospective and longitudinal designs, and examination of structure-function associations.

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Contents

1. Introduction

Adolescence, spanning from around the time of pubertal onset, roughly age 9–12 (Crone and Dahl, 2012), until the early- to mid–20s (Crews et al., 2007; Spear, 2000), is a period of dramatic neuroplasticity when widespread developmental changes in neural structure and function are thought to underlie improvements in cognitive, affective, and social domains (Andersen, 2003; Casey, 2015; Luna et al., 2015). In particular, maturation of macroscopic brain networks, through a combination of developing neurotransmitter systems (Gomes et al., 2016), improved white matter microstructural integrity and changing patterns of task-related and intrinsic neural dynamics, promotes the computational specialization of the neural circuitry necessary to meet the demands of an individual's environment (Luna et al., 2015). Importantly, this period of plasticity coincides with a dramatic rise in the incidence of several forms of serious psychiatric illness, including depression, that are thought to arise when the typical course of adolescent brain development is disrupted (Paus et al., 2008). Despite extensive investigation of human development and psychopathology, the precise neurobiological pathways underlying the emergence of depression, a common, recurrent, and serious form of psychopathology that typically begins during adolescence (Davey et al., 2008), still remain poorly understood. Elucidating the neurodevelopmental processes that lay the foundation for adaptive adolescent functioning will aid in the identification of neural markers that predict risk for adolescent psychopathology and guide the design of novel prevention and intervention approaches.

1.1. Goals of the current review

Here, we posit that connectivity of the anterior cingulate cortex (ACC) as a key neural substrate of adolescent neurodevelopment that supports the development of adult self-regulatory capabilities and that can contribute to psychopathology during adolescence when its development is aberrant. Because of the ACC's location, role as a hub for global neural network dynamics, and critical function in integrating multimodal cognitive, affective, and social information to guide adaptive affect and behavioral regulation (Shenhav et al., 2013), we hypothesize that healthy development of ACC is essential for mental health as young people proceed through adolescence and into adulthood. Additionally, because altered affect regulation is a fundamental characteristic of depression, we propose that both structural and functional connectivity of this essential region are altered in adolescents with depression. This focus stands in contrast to prior work on the developmental

neuroscience of adolescent psychopathology, which has primarily focused on either global developmental changes (Giedd et al., 2015; Power et al., 2010; Uda et al., 2015), such as decreasing volume of gray matter over adolescence, or the protracted development of the prefrontal cortex and its potential functional consequences for disorders involving self-regulation (Casey, 2015; Geier, 2013). Similarly, conceptual papers on the function of the ACC have neglected its relevance to adolescent development and developmental psychopathology (Drevets et al., 2008; Shenhav et al., 2013; Weston, 2012). In all, the extant body of literature has failed to appreciate the unique and critical role of the ACC in adolescent brain and behavioral development.

To support our hypothesis, we present a meta-analysis of white matter development during adolescence in two tracts that are central to structural connectivity of the ACC: the cingulum and the anterior thalamic radiations (ATR). Thus, we integrate findings across the large number of developmental studies using diffusion tensor imaging (DTI) to assess white matter microstructure. Although there is a rich cross-sectional literature examining age effects on white matter microstructure, there is a much smaller body of research using longitudinal data to address developmental changes in white matter across adolescence. Extant longitudinal work is limited by a small number of follow-up assessments, short inter-scan intervals, and inconsistency in the white matter tracts included. Furthermore, although many studies have examined patterns of white matter development across the lifespan, very few have focused specifically on adolescence in order to characterize the trajectory of microstructural changes during this critical developmental period. Therefore, the present meta-analysis aims to more clearly delineate the pattern of cingulum and ATR development in adolescence to establish whether microstructure of these pathways continues to mature throughout this period.

Next, we provide a critical, integrative review of the development of functional connectivity of the ACC. As this literature does not readily lend itself to meta-analytic techniques because of the variety of data analytic strategies applied, we limit our review to a discussion and interpretation of findings across studies. We then extend the consideration of ACC connectivity during adolescence to depression. Depression emerges during adolescence and is most consistently related to ACC structure and function, and its core feature—altered affect regulation—is conceptually linked to a primary function of the ACC (Pizzagalli, 2011; Rive et al., 2013). Finally, we identify gaps in the literature and weaknesses in studies to date, providing recommendations for future research. Throughout, we use a framework of developmental psychopathology, which approaches adolescence as a vulnerable period during

which typical development must be understood as a foundation for the deviations that result in atypical development.

1.2. The anterior cingulate cortex (ACC)

The ACC, or the anterior portion of the medial cerebral cortex that lies below the frontal cortex and superior to the corpus callosum (Nolte, 2008), is hypothesized to play a central role in processing information from a broad range of domains in order to guide adaptive behavior (Gasquoine, 2013; Holroyd and Yeung, 2012; Lavin et al., 2013; Shenhav et al., 2013; Weston, 2012). Overall, the ACC is active during a wide range of contexts and has been implicated in an array of different functions, including error and conflict monitoring (Botvinick et al., 2004), affective processing (Etkin et al., 2011), social processing (Beckmann et al., 2009), and reward learning and decision-making (Haber and Behrens, 2014). Several recent reviews have sought to integrate these seemingly diverse functions of the ACC into an overarching function, suggesting that the ACC compiles multimodal information (Lavin et al., 2013; Luna et al., 2015; Shackman et al., 2011; Shenhav et al., 2013) in order to estimate the cognitive and behavioral requirements of different responses (Shenhav et al., 2013; Weston, 2012) and adaptively select and maintain behavioral options (Gasquoine, 2013; Holroyd and Yeung, 2012). A common feature of these accounts is their designation of the ACC as a hub for information processing that integrates inputs from multiple domains and systems: affective, social, cognitive, and visceral (Gasquoine, 2013; Holroyd and Yeung, 2012; Lavin et al., 2013; Luna et al., 2015; Shackman et al., 2011; Shenhav et al., 2013; Weston, 2012). Based on this integration, the ACC is postulated to drive activation in premotor and motor cortical regions as well as basal ganglia, cerebellum and PFC to guide cognitive and behavioral output (Shenhav et al., 2013; Weston, 2012). Given its putative role as the hub connecting multimodal inputs and sophisticated outputs, connectivity between the ACC and other cortical and subcortical brain regions is of particular interest for adolescent development.

The ACC can be further subdivided into subgenual, rostral, and dorsal regions, which are thought to have distinct functional specializations, with a transition along a dorsal to rostral continuum from cognitive to affective processes (Mohanty et al., 2007). The subgenual ACC (sgACC), located ventral to the genu of the corpus callosum (also referred to as the ventral ACC), has been strongly implicated in the automatic modulation of affect (Drevets et al., 2008; Phillips et al., 2008). This region is thought to correspond to the infralimbic cortex in the rodent brain (Öngür and Price, 2000). The dorsal ACC (dACC) is comprised of the cingulate gyrus and sulcus from the genu of the corpus callosum to the plane of the anterior commissure (also known as the midcingulate cortex) and interacts with motor regions to select actions based on integrated information about long term goals and reward contingencies (Rive et al., 2013; Shackman et al., 2011; Shenhav et al., 2013). This region of the ACC is thought to be unique to humans and has no homologous regions in the primate or rodent brain (Vogt et al., 2013). The rostral ACC (rACC; also referred to as pregenual ACC), situated anterior to the genu of the corpus callosum, shows strong connectivity with both dorsal and subgenual divisions and is hypothesized to coordinate autonomic, visceromotor, and endocrine components of affective responses (Sturm et al., 2013). The rACC is considered homologous to rodent ACC (i.e., area d32), although some cytoarchitectural distinctions have been noted between species (Vogt et al., 2013).

1.3. ACC and the development of adaptive self-regulation

Adolescence is an important period for the development of adaptive self-regulation – the ability to monitor and modify one's reactions to meet one's goals (Thompson, 1994) – which facilitates improved interpersonal functioning and the establishment of long-term objectives as individuals make the transition to adult status and roles (Farley and Kim-Spoon, 2014). Adolescence is widely conceptualized as a time of social-affective reorientation (Blakemore and Mills, 2014; Crone and Dahl, 2012; Somerville et al., 2010). Across this period, youth develop increased independence, form more intimate friendships, begin romantic relationships, become strongly aware of their status among peers, and are subject to increasing educational and occupational demands that necessitate increasingly complex self-regulatory capabilities. Therefore, the development of mature self-regulation is a critical task of adolescence, as it is required to achieve many of the central goals of adulthood. These include obtaining an education, contributing to the workforce, initiating and maintaining romantic relationships, forming a supportive social network, and regulating behavior in order to thrive in multiple domains (Brown et al., 2008; Pfeifer et al., 2011; Schulenberg et al., 2004).

In particular, adolescents have been shown to make more maladaptive or "risky" decisions in the presence of peers (Chein et al., 2011) and in affectively arousing contexts (Figner et al., 2009) relative to adults. Age-related improvements in decision-making in social and affective contexts are hypothesized to derive from neurodevelopmental changes in regions related to estimating reward value of environmental information and developing interactions between subcortical and cortical systems that support aspects of decision making that rely on complex cost-benefit calculations (Hartley and Somerville, 2015). Given the putative role of the ACC in integrating affective, social and cognitive information to guide action selection, maturation of ACC connectivity is a likely mechanism supporting more adaptive self-regulation and decision-making under such complex cost-benefit scenarios.

In addition to supporting typical adolescent development, developing ACC connectivity has important implications for risk for psychopathology during this period. In particular, ACC dysfunction has been strongly implicated in depression in both adult and adolescent samples. Depression is characterized by difficulty modulating negative affect, as well as a decrease in goal-directed behaviors, functions that are closely tied to ACC function. Congruently, a recent meta-analysis including over 500 participants demonstrated that depressed youth display aberrant activation in both dorsal and subgenual ACC (Miller et al., 2015). Furthermore, direct modulation of subgenual ACC function has been identified as a promising treatment for depression (Berlim et al., 2014), suggesting that disrupted ACC function is a fundamental feature of the disorder that may play a causal role in the onset and maintenance of depression.

1.4. Structural and functional connectivity of the ACC

Given the ACC's role as a hub for processing and integrating many types of information (van den Heuvel and Sporns, 2013), the development of its structural and functional connectivity of this region may be a neural mechanism of adaptive self-regulation in adolescence.

1.4.1. Structural ACC connectivity
The ACC sits at the intersection of the brain's cognitive, affective, and action networks (Haber and Behrens, 2014) and is directly connected to limbic and subcortical structures as well as prefrontal and motor cortical regions (Beckmann et al., 2009). The current review focuses on the cingulum bundle and anterior thalamic radiations, as these represent the primary white matter pathways linking the ACC with its distributed afferent and efferent targets.
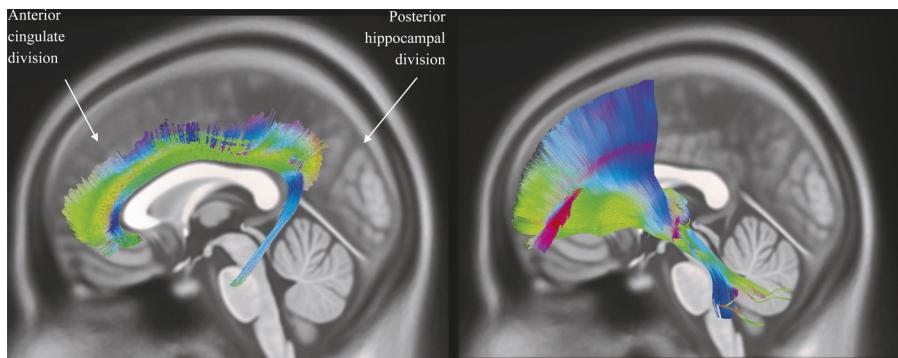
Fig. 1. Illustration of the (a) cingulum and (b) anterior thalamic radiations (ATR). Original figure generated to illustrate the pathways of interest in the current review. Deterministic tractography was used to track the cingulum and ATR using diffusion spectrum imaging data from an atlas generated from a sample of 60 neurologically healthy participants (the sample and atlas generation process are described in Jarbo and Verstynen, 2015; Yeh et al., 2016). Color-coded images show the orientation of the principal direction of diffusion of each streamline, with red, blue, and green representing diffusion along x-, y-, and z-axes, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

1.4.1.1. Cingulum. The cingulum bundle is a major white matter pathway that runs along the anterior-posterior axis of each hemisphere and facilitates communication between frontal, parietal, and temporal cortices as well as subcortical structures, including the striatum and hippocampus (See Fig. 1). Based on the topography of cingulum fibers, this pathway can be divided into subgenual, dorsal, and parahippocampal/temporal sections that differ with regard to their spatial location, microstructural characteristics, and connectivity profiles (Jones et al., 2013). Based on these subdivisions, several studies of adolescent development divide this pathway into its anterior cingulate and posterior hippocampal components (e.g., Rollins et al., 2010; Simmonds et al., 2014). In these instances, the current meta-analysis will focus on age-related changes in the anterior cingulate division of the cingulum, containing fibers that connect subgenual and dorsal regions of the ACC to other anterior and posterior cingulate regions, prefrontal, motor, temporal, and parietal cortical areas, as well as subcortical structures including the amygdala, hippocampus, striatum, and hypothalamus (Beckmann et al., 2009; Heilbronner and Haber, 2014; Jones et al., 2013).

1.4.1.2. Anterior thalamic radiations (ATR). The ATR is the primary conduit for communication between the ACC and subcortical limbic structures. This pathway links the anterior thalamic nuclei and the ACC and medial frontal regions via the anterior limb of the internal capsule and anterior corona radiata (Catani and Thiebaut de Schotten, 2012; Lobel et al., 2009) (See Fig. 1). The anterior thalamic nuclei are considered to be part of the limbic system, as they receive input from the hippocampus and hypothalamic mammillary bodies (Catani and Thiebaut de Schotten, 2012). Therefore, the ATR facilitates the integration of affective and visceral information with other cognitive functions of the ACC.

Different studies of structural connectivity across development examine distinct portions of this pathway, including the anterior limb of the internal capsule (i.e. Lebel et al., 2008), anterior corona radiata (i.e. Verhoeven et al., 2010), and/or applying tractography to define the ATR (i.e. Peters et al., 2012), each of which will be included in the current meta-analysis. However, it is important to note that the anterior limb of the internal capsule and anterior corona radiata contain frontostriatal and frontopontine fibers in addition to anterior thalamic projections (Catani and Thiebaut de Schotten, 2012). Therefore, developmental changes in the anterior limb of the internal capsule and anterior corona radiata may not be specific to the ATR, and must be interpreted with caution.

1.4.1.3. Measuring structural ACC connectivity. Diffusion MRI is a neuroimaging method that quantifies structural connectivity by measuring the direction and magnitude of water diffusion in neural tissue (Dell'Acqua and Catani, 2012; Hagmann et al., 2006). Fractional anisotropy (FA) is the most common diffusion MRI-based measure of white matter microstructure, with higher values indicative of greater structural integrity and improved organization, cohesion, and compactness of white matter fiber tracts (Beaulieu, 2002; Bonekamp et al., 2007; Paus, 2010; Walhovd et al., 2014). Several other metrics can also be calculated, including *mean diffusivity* (MD), which estimates of the overall magnitude of diffusion, *axial diffusivity* (AD), which measures diffusion along the primary direction of diffusion, and *radial diffusivity (RD)*, which reflects the amount of diffusion perpendicular to the primary diffusion direction. Although the precise cellular mechanisms of change in each diffusion metric remain unclear, higher FA and AD coupled with lower RD and MD are generally considered to reflect better structural integrity, increased myelination, and greater cohesion of white matter pathways.

1.4.2. Functional ACC connectivity

In addition to its direct structural connections, the ACC plays a central role in two of the basic functional neural networks: the default mode network (DMN) and the salience network (SN). The DMN is a canonical resting-state network that includes the medial prefrontal cortex, posterior cingulate cortex, lateral parietal cortex and rACC (Greicius et al., 2003; Raichle, 2015), and that has been implicated in an array of functions related to self-referential mental activity, including autobiographical memory, self-monitoring, self-regulation, and source monitoring (Fair et al., 2008; Northoff, 2014), as well as related social cognitive functions (Spreng et al., 2009). Perhaps not surprisingly, serious psychopathology is associated with hyperactive, hyperconnected DMN (Broyd et al., 2009; Whitfield-Gabrieli and Ford, 2012). The salience network (SN) is a neural network primarily comprised of the dACC and anterior insula, which has been implicated in the identification of salient internal and external stimuli to guide behavior (Menon and Uddin, 2010).

Further supporting the central role of the ACC in integrating across multiple domains, seed-based approaches have demonstrated that resting-state functional connectivity of the ACC is distributed widely throughout the brain. Dorsal activation is correlated with activation of sensorimotor circuits, rostral activity is linked to PFC activation, and transitional zones of connectivity appear to be functionally connected to both prefrontal and sensorimotor brain regions and promote coordination among these networks (Margulies et al., 2007). Therefore, based on its structural and functional connectivity, the ACC is uniquely well equipped to

process multimodal information and to integrate this information to guide adaptive behavior.

1.4.2.1. Measuring functional ACC connectivity. Functional connectivity MRI (fcMRI) is a method of inferring functional connectivity between different brain regions based on temporal correlations in neural signal during the performance of a task or at rest (Power et al., 2010). Temporal coherence in spontaneous low-frequency signal fluctuations at rest is hypothesized to reflect a history of co-activation suggesting a functional relationship between regions (Ernst et al., 2015). Several statistical methods have been applied to fcMRI data, including seed-based approaches, (e.g., psychophysiologic interaction), graph analysis techniques on region-to-region connectivity, and independent/principal component analysis (Power et al., 2010), which vary in the degree to which they are hypothesis- or data-driven (Ernst et al., 2015). Seed-based approaches select a small number of regions *a priori* and assess correlations between fluctuations the signal in these regions and fluctuations in voxels throughout the rest of the brain. Graph theory methods involve parcellating the brain into a large number of different regions, or "nodes", and simultaneously analyzing pairwise correlations in coordination, or "edges", between each node and other nodes. Finally, studies using independent/principal component analysis use decomposition methods to group regions based on their temporal coherence in neural signal. In the current review, we will include studies using all types of fcMRI analysis.

1.5. ACC connectivity and developmental psychopathology

Based on its critical role in promoting self regulation, the development of ACC connectivity is likely to play an important role in the development of depression during adolescence. The most compelling developmental psychopathology model of depression proposes that depression emerges during adolescence because of the occurrence of the simultaneous development in multiple, interacting domains (Davey et al., 2008). Specifically, dramatic changes in peer social orientation, neural reward circuitry, executive function, reward motivation, and self-relevant goals during adolescence are postulated to combine, in vulnerable youth, to create a foundation for depression. Congruently, a recent meta-analytic review of neural response in adolescent depression reported that ACC is consistently disrupted across a variety of task contexts (Miller et al., 2015). At a network level, studies have consistently found that depression is associated with enhanced connectivity within the anterior DMN (including the rACC) (Kaiser et al., 2015; Mulders et al., 2015) and reduced connectivity between the DMN and the frontoparietal control network (Mulders et al., 2015).

2. Typical development of structural ACC connectivity: meta-analysis

2.1. Methods

2.1.1. Study selection

For the purposes of the current review, we chose to include studies with human participants from age 10–20 (at minimum) and tested the effect of age on FA of the cingulum and/or ATR. Adolescence is broadly defined as the transitional period between childhood and adulthood (Crone and Dahl, 2012), but the precise onset and offset of adolescence are difficult to delineate (Spear, 2000). Traditionally, this period is thought to begin around the time of pubertal onset, roughly age 9–12 (Crone and Dahl, 2012) and end with relative independence from the parents (Casey, 2015) during the early- to mid–20 s (Crews et al., 2007; Spear, 2000). Because studies of adolescent development have varied considerably in the age groups they include or have examined development in a wider

range of the lifespan, many of the studies included an age range broader than 10–20 years.

We conducted literature searches with PubMed, Google Scholar, and Ovid Medline using search terms adolescen*, (development* OR maturation OR age-related), and (diffusion AND (weighted OR tensor)) OR (DTI OR TBSS). Reference lists were also examined to identify additional studies meeting these inclusion criteria. Using this search strategy, 37 studies were identified that met our inclusion criteria. From the total body of studies identified, those reporting regression coefficients corresponding to the linear, quadratic, or logarithmic effect of age on FA of the cingulum (N = 10 studies) and/or ATR (N = 7 studies) were selected for inclusion in the meta-analysis.

2.1.2. Data analysis

From all relevant studies, we extracted the reported regression coefficient for the influence of age on multiple DTI-based diffusivity measures (e.g., FA) and used these parameters to simulate a predicted trajectory of different white matter metrics across the range of ages included in each study. For studies reporting linear effects of age, a linear model was used to simulate metrics of white matter microstructure at each age, whereas for studies reporting quadratic effects of age, a quadratic model was used. In instances when studies parcellated the cingulum into anterior and posterior (hippocampal) divisions, only diffusivity metrics corresponding to the anterior region were selected for inclusion. For the ATR, diffusivity measures were included that correspond to the anterior limb of the internal capsule, anterior corona radiata, and the ATR as a whole. For studies reporting results from multiple regression models (i.e. linear and quadratic models), separate datasets were generated for each model. FA values were converted to z-scores in order to standardize across studies, producing an estimate of the predicted direction and relative magnitude of change in FA at each age for each pathway (See Fig. 2). Simulated data from each regression model from each study were aggregated to form a composite dataset of simulated white matter integrity across development and linear and quadratic effects of age on FA were tested on this composite set. Each study was dummy coded and included as a covariate to control for variation across study samples and methods, as well as to account for the fact that some studies contributed multiple data points to the analysis. The likelihood ratio test was used to determine whether the quadratic model was a significantly better fit to the data relative to the linear model for each study. Finally, linear and quadratic regression models were also applied within the 10–20 age range, in order to specifically assess the direction, trajectory, and significance of change in white matter microstructure during adolescence. The same method was used to combine across studies that reported regression coefficients for mean, radial, and axial diffusivity of the cingulum and/or ATR.

2.2. Results

2.2.1. Cingulum

We identified 10 studies of age associations with white matter microstructure of the cingulum bundle, which also reported regression coefficients corresponding to general linear regression models. Three studies included multiple regression models, resulting in a total of 13 models included in the current meta-analysis (See bolded studies in Table 1 and results in Table 2).

2.2.1.1. FA. Across all 13 models, significant effects of age were found for the linear (beta = −0.474, $p < 0.001$) and quadratic (age beta = 1.597, $p < 0.001$; age^2 beta = −2.096, $p < 0.001$) regression models. The likelihood ratio test demonstrated that the quadratic model was a better fit to the data including the entire range of ages (deviance = 139.33, $p < 0.05$). Looking specifically at the
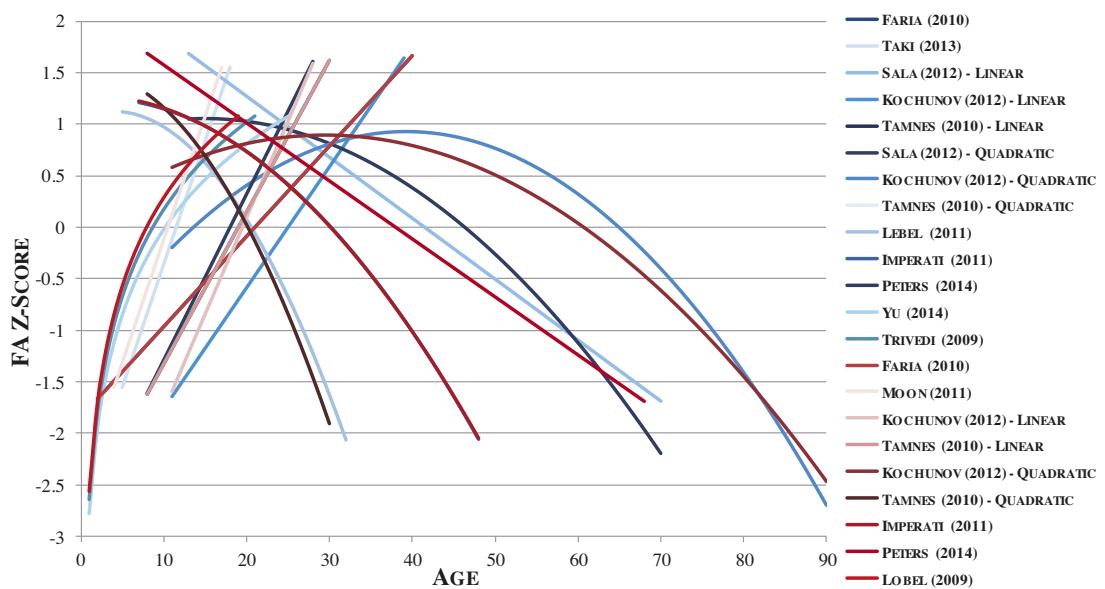
Fig. 2. Illustration of meta-analysis methods. Regression models reported for each pathway were used to simulate fractional anisotropy (FA) data for each age within the range included in each study. FA values were converted to z-scores in order to standardize across studies, producing an estimate of the predicted direction and magnitude of change in FA at each age for each pathway. Blue lines represent regression models of developmental change in FA of the cingulum. Red lines represent regression models for age effects on FA in the anterior thalamic radiations. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

adolescent period (age 10–20), a significant linear (beta = 0.218, $p < 0.001$) and trend-level quadratic (age beta = 0.835, $p = 0.021$; age^2 beta = −0.619, $p = 0.084$) effect of age on FA was also observed. In this case, the quadratic model was not a significantly better fit to the data (deviance = 0.282, NS), and the linear model was retained (See Fig. 3).

2.2.1.2. MD, RD, and AD. Four studies reported regression coefficients for the effect of age on non-FA diffusivity metrics MD, RD, and AD. Two studies contributed 2 models, resulting in a total of 6 models for inclusion. Across the age range included, significant linear and quadratic effects of age were found for each measure (all $p < 0.001$), and the quadratic models were found to fit the data better (all $p < 0.05$; see Table 2 for full results). Additionally, within the adolescent period (age 10–20), significant linear effects of age were observed for MD, RD, and AD (all $p < 0.01$), whereas quadratic age effects were not significant (See Fig. 4).

2.2.2. ATR

Seven studies reported regression coefficients for age effects on white matter microstructure of the ATR, contributing a total of 9 regression models (See bolded studies in Table 1 and results in Table 3).

2.2.2.1. FA. Across the entire age range (age 0–90), significant linear (beta = −0.7, $p < 0.001$) and quadratic (age beta = 0.903, $p < 0.001$; age^2 beta = −1.616, $p < 0.001$) effects of age were found. Again, the quadratic model was found to be a better fit to the data (deviance = 49.232, $p < 0.05$). Within adolescence (age 10–20), a significant linear (beta = 0.168, $p < 0.001$) effect of age was present, whereas quadratic terms were not significant (See Fig. 3).

2.2.2.2. MD, RD, and AD. Only 1 study included in the literature review reported regression coefficients for MD, so this measure was excluded from the meta-analysis. Three studies provided a total of 4 models testing age effects on ATR RD and AD. Linear effects of age were found for both (both $p < 0.001$), whereas quadratic effects were only found for AD (See Table 3 for full results). Within ado-

lescence, linear decreases in both RD and AD were found (both $p < 0.01$).

2.3. Summary of typical development of structural ACC connectivity

Collectively, results of the literature review and meta-analysis converge in reporting a curvilinear course of cingulum and ATR development, characterized by increasing FA across adolescence that peaks in the third decade of life (See Fig. 3). An inverse pattern of developmental trajectories was seen for MD and RD measures, suggesting that the age-related effects on white matter pathways relates, in part, to changes in underlying myelination integrity (Budde et al., 2009; Song et al., 2005). Additionally, these findings suggest that microstructural development may progress at different rates at different points in adolescence, and future research should explore how variation in the trajectory of white matter development may relate to the development of cognitive, affective, and social skill across adolescence.

3. Typical development of functional ACC connectivity: review

Throughout the brain—but particularly for the ACC—patterns of functional connectivity undergo ongoing remodeling between childhood and adulthood. Adolescent brain development features the increasing prominence of the ACC in the brain's functional networks. Overall, a transition from local to distributed connectivity takes place, whereby children show greater resting-state connectivity between local regions and adults display a more distributed pattern of long-range connectivity throughout the brain (Power et al., 2010). Furthermore, several distinct neural networks strengthen their connectivity while others weaken across development (Ernst et al., 2015).

White matter pathways connect a majority of common neural networks (van den Heuvel et al., 2009), but regions can also display strong functional connectivity in the absence of known structural connections (Honey et al., 2009). Therefore, within a given network,

Table 1
Diffusion tensor imaging studies of typical development of FA within the cingulum and anterior thalamic radiations.

	N	Age	FA Change[a]	T	b-value	Directions	Cingulum ROI	ATR ROI
Longitudinal Region-of-Interest Studies								
Brouwer et al. (2012)	126	9–12	↑	1.5	1000	32	Yes	–
Lebel and Beaulieu, 2011 (2011)	**103**	**5–32**	↑	1.5	1000	6	Yes	–
Simmonds et al. (2014)	128	8–29	↑	3	800	6	Yes	Yes
Cross-sectional Region-of-Interest Studies								
Bonekamp et al. (2007)	40	5–19	↑	1.5	1000	15	Yes	Yes
Cancelliere et al. (2013)	202	0–18	–	1.5	1000	15	–	Yes
Clayden et al. (2012)	53	8–16	↑	1.5	1000	20	Yes	Yes
Faria (2010)	**35**	**2–40**	↑	**1.5**	**700**	**32**	**Yes**	**Yes**
Grieve et al. (2011)	213	7–86	↑	1.5	1250	12	Yes	–
Imperati et al. (2011)	**144**	**7–48**	↑	**3**	**1000**	**64**	**Yes**	**Yes**
Kochunov et al. (2012)	**831**	**11–90**	↑	**3**	**700**	**55**	**Yes**	**Yes**
Lebel et al. (2008)	202	5–30	↑	1.5	1000	6	Yes	Yes
Lebel et al. (2012)	403	5–83	↑	1.5	1000	6	Yes	Yes
Lobel et al. (2009)	**72**	**0–19**	↑	**1.5**	**1000**	**6**	–	**Yes**
Moon et al. (2011)	**87**	**4–17**	↑	**3**	**1000**	**6**	–	**Yes**
Peters et al. (2014)	**296**	**8–68**	↑↓[b]	**3**	**1000**	**31**	**Yes**	**Yes**
Qiu (2008)	75	6–26	↑	3	1000	6	–	Yes
Rollins et al. (2010)	32	6–18	↑	3	700	30	Yes	Yes
Sala (2012)	84	13–70	↓	1.5	900	12	Yes	–
Snook (2005)	60	8–27	↑	1.5	1000	6	–	Yes
Stadlbauer (2008)	38	18–88	–	3	1000	6	Yes	–
Supekar et al. (2010)	33	7–22	↑	3	850	23	Yes	–
Taki (2013)	**290**	**5–18**	↑	**3**	**1000**	**32**	**Yes**	–
Tamnes (2010)	**168**	**8–30**	↑	**1.5**	**700**	**30**	**Yes**	–
Trivedi (2009)	**51**	**0–21**	↑	**1.5**	**700 & 1000**	**10**	**Yes**	–
Verhoeven et al. (2010)	78	0–24	↑	3	800	45	Yes	Yes
Westlye (2010)	430	8–85	↑	1.5	700	30	Yes	Yes
Yu (2014)	**65**	**0–25**	↑	**3**	**1000**	**30**	**Yes**	–
Longitudinal Voxelwise Studies							Cingulum Sig	ATR Sig
Bava (2010)	22	16–21	↑	3	2000	15	–	Yes
Giorgio (2010)	24	13–18	↑	1.5	1000	60	Yes	Yes
Wang (2012)	16	13–17	↑	1.5	1000	32	Yes	Yes
Cross-sectional Voxelwise Studies								
Ashtari (2007)	24	10–20	↑	1.5	1000	25	Yes	–
Barnea-Goralay (2005)	34	6–19	–	1.5	900	6	–	Yes
Brauer (2011)	20	5–32	↑	1.5	1000	60	Yes	Yes
Faria (2010)	Listed above						–	–
Giorgio (2008)	42	13.5–42	–	1.5	1000	60	–	–
Peters et al. (2012)	78	8–21	↑	1.5	1000	31	Yes	Yes
Qiu (2008)	Listed above						Yes	Yes
Qiu (2010)	96	11–25	↑	3	1000	12	Yes	Yes
Schmithorst et al. (2002)	33	5 – 18	–	3	814/994	6	–	Yes
Stevens et al. (2009)	50	11–37	↑	3	1000	12	–	–
Taki (2013)	Listed above						–	–

Note. Studies included in the meta-analysis are **bolded**. Characteristics of studies reporting both ROI and voxelwise analyses are listed only once.
  [a] The direction of FA change refers to the adolescent period, not lifespan change.
  [b] Peters et al. (2012) found increased FA of the cingulum, and decreased FA for the ATR.

some regions may be directly connected via major white matter tracts, whereas others may take several steps to communicate with one another. Importantly, when known structural connections are present, white matter microstructure has been shown to predict functional connectivity (Damoiseaux and Greicius, 2009; Honey et al., 2009). Thus, improved white matter integrity of the cingulum and ATR may directly strengthen functional connectivity of the ACC and contribute to improved integration between cognitive, affective, and social domains. Functional connections associated with higher-level social-cognitive and affective functions show a more protracted developmental course than connections related to motor and attentional control, supporting the notion that age-related changes in functional ACC connectivity may underlie the maturation of key higher-level capabilities across adolescence.

3.1. Development of default mode and salience network connectivity

The DMN and SN both show a strong developmental pattern of increasing functional network connectivity across adolescence. Consistent with the dorsal to rostral continuum of cognitive and affective functions of the ACC (Mohanty et al., 2007), the sgACC and rACC become more strongly connected to the DMN, whereas dACC shows increasing connectivity with the SN during this period. Within the DMN, regions display only limited connectivity in childhood and become strongly functional connected by adulthood (Fair et al., 2008). In particular, anterior DMN connectivity of the rACC was shown to increase significantly between age 7 and 18 (Sole-Padulles et al., 2016). Similarly, looking at connectivity of the SN across development, significantly stronger functional connectivity between the dACC and anterior insula has been observed among adults relative to children (Uddin et al., 2011), with dACC connectivity increasing significantly between age 7–18 (Sole-Padulles et al., 2016). Furthermore, a direct comparison of structural and functional connectivity of the DMN across development identified the cingulum to be the most immature link in this network in childhood, and demonstrated that cingulum FA was positively correlated with DMN functional connectivity in adulthood (Supekar et al., 2010). Therefore, ongoing development of cingulum microstructure in adolescence may contribute to increased

Table 2
Meta-analytic results for linear and quadratic effects of age on cingulum microstructure.

Model	# Studies	# Models	Age Range	Beta (Age)	p	Beta (Age2)	p	R^2	Adjusted R^2	SS_E
FA										
Linear	10	13	1–90	−0.474	0.001	–	–	0.119	0.094	427.95
Quadratic	**10**	**13**	**1–90**	**1.597**	**.001**	**−2.096**	**.001**	**0.406**	**0.388**	**288.621***
Linear	**10**	**13**	**10–20**	**0.218**	**.001**	**–**	**–**	**0.859**	**0.844**	**12.173**
Quadratic	10	13	10–20	0.834	0.021	0.619	0.084	0.862	0.846	11.891
MD										
Linear	4	6	1–70	0.512	0.001	–	–	0.137	0.11	168.277
Quadratic	**4**	**6**	**1–70**	**−2.485**	**.001**	**2.841**	**.001**	**0.472**	**0.453**	**102.886***
Linear	**4**	**6**	**10–20**	**−0.23**	**.001**	**–**	**–**	**0.836**	**0.817**	**7.313**
Quadratic	4	6	10–20	−0.95	0.122	0.722	0.236	0.841	0.818	7.109
AD										
Linear	4	6	1–70	−0.983	0.001	–	–	0.547	0.534	99.68
Quadratic	**4**	**6**	**1–70**	**−2.105**	**.001**	**1.112**	**.001**	**0.615**	**0.602**	**84.788***
Linear	**4**	**6**	**10–20**	**−0.151**	**.002**	**–**	**–**	**0.897**	**0.885**	**5.795**
Quadratic	4	6	10–20	0.263	0.551	−0.415	0.389	0.898	0.885	5.712
RD										
Linear	4	6	1–70	0.509	0.001	–	–	0.146	0.123	187.807
Quadratic	**4**	**6**	**1–70**	**−2.421**	**.001**	**2.904**	**.001**	**0.608**	**0.595**	**86.245***
Linear	**4**	**6**	**10–20**	**−0.173**	**.002**	**–**	**–**	**0.862**	**0.846**	**4.78**
Quadratic	4	6	10–20	−0.618	0.270	0.445	0.424	0.864	0.845	4.721

Note. Boldface text indicates model with better fit according to likelihood ratio test.

Table 3
Meta-analytic results for linear and quadratic effect of age on white matter microstructure of anterior thalamic radiation.

Model	# Studies	# Models	Age Range	Beta (Age)	p	Beta (Age2)	p	R^2	Adjusted R^2	SS_E
FA										
Linear	7	9	1–90	−0.7	0.001	–	–	0.272	0.251	225.691
Quadratic	**7**	**9**	**1–90**	**0.903**	**.001**	**−1.616**	**.001**	**0.431**	**.412**	**176.459***
Linear	**7**	**9**	**10–20**	**0.168**	**.001**	**–**	**–**	**0.842**	**0.824**	**9.55**
Quadratic	7	9	10–20	0.588	0.218	−0.422	0.377	0.843	0.824	9.459
MD – Only 1 study reported regression coefficients corresponding to age effect on MD										
AD										
Linear	3	4	1–40	−0.807	0.001	–	–	0.536	0.517	46.401
Quadratic	**3**	**4**	**1–40**	**0.508**	**.052**	**−1.351**	**.001**	**0.638**	**0.62**	**36.162***
Linear	**3**	**4**	**10–20**	**−0.655**	**.001**	**–**	**–**	**0.467**	**0.411**	**2.969**
Quadratic	3	4	10–20	0.836	0.516	−1.499	0.248	0.486	0.417	2.862
RD										
Linear	**3**	**4**	**1–40**	**−0.672**	**.001**	**–**	**–**	**.372**	**0.347**	**62.764**
Quadratic	3	4	1–40	−1.092	0.002	0.432	0.201	0.383	0.351	61.72
Linear	**3**	**4**	**10–20**	**−0.216**	**.005**	**–**	**–**	**0.805**	**0.785**	**4.285**
Quadratic	3	4	10–20	−0.549	0.488	0.334	0.672	0.806	0.78	4.264

Note. Only 1 study reported regression coefficients for MD so this measure was excluded from the meta-analysis for the anterior thalamic radiations. Boldface text indicates model with better fit according to likelihood ratio test.

functional connectivity of the DMN, and facilitate the self- and social-cognitive functions this network supports.

4. ACC connectivity and adolescent depression

Building on the meta-analytic and literature review findings that the ACC's structural and functional connectivity develop substantially during adolescence, we turn to the role of ACC connectivity in the development of depression in adolescence. We review the findings from DTI and fcMRI studies (both resting-state and task-based approaches), with attention to young people with clinical-level psychopathology or at risk for psychopathology, primarily because of family history. We searched for studies of functional connectivity during task or resting contexts in adolescents (age 10–20) with depression (Table 4). We did not exclude studies based on tech-

nique for computing functional connectivity or for focus on ACC as a seed region. We did not include treatment studies or studies focusing on remitted depression, as they address questions different from those we are posing.

4.1. Structural ACC connectivity

4.1.1. Adolescents at high risk for depression

Among adolescents at high familial risk for depression, two previous studies have identified decreased FA of the cingulum relative to adolescents with no family history of mood disorder (Huang et al., 2011; Keedwell et al., 2012). These results support the hypothesis that aberrant cingulum microstructure may confer greater risk for MDD. However, given the preliminary nature of the

Table 4
Structural and functional ACC connectivity in adolescent depression.

Structural Connectivity								
Adolescents at High Risk for Depression								
	HR *n*	LR *n*	Mean Age	FA Difference	Tract	T	b-value	Directions
Huang et al. (2011)	18	13	15.6	↓	Cingulum	3	1000	30
Keedwell et al. (2012)	18	15	22.2	↓	Cingulum	3	1000	30
Adolescents with Depression								
	MD *n*	TD *n*	Mean Age	FA Difference	Tract	T	b-value	Directions
Cullen et al. (2010)	14	14	16.8	↓	Cingulum	3	1000	30
Henderson et al. (2013)	17	16	16.6	↓	Cingulum, ATR	3	1000	12
LeWinn et al. (2014)	52	42	16.1	↓	ATR	3	1500	30

Functional Connectivity								
Adolescents at High Risk for Depression								
	HR *n*	LR *n*	Mean Age	ACC Connectivity	Regions with Connectivity to ACC	Subregion	Context	Method
Chai et al. (2015)	27	16	11.2	↓ ↑	dlPFC mPFC/PCC	sgACC	Rest	mPFC/PCC, dlPFC, amygdala seeds
Clasen et al. (2014)	11	13	13.6	↓	rIFG	dACC	Rest	rIFG seed
Kerestes et al. (2016)	29	43	14	–	–	–	Viewing happy faces	Putamen, dlPFC seeds
Adolescents with Depressive Symptoms								
	n		Mean Age	ACC Connectivity	Regions with Connectivity to ACC	Subregion	Context	Method
Strikwerda-Brown et al. (2015)	72		16.47	↓	PCC, angular gyrus, dlPFC, dmPFC, vmPFC	sgACC	Rest	sgACC seed
Davey et al. (2015)	56		16.5	↑	Amygdala	sgACC	Rest	Amygdala seed
Adolescents with Current Depression								
	MD N	TD N	Mean Age	ACC Connectivity	Regions with Connectivity to ACC	Subregion	Context	Method
Connolly et al. (2013)	23	36	16	↑	Insula, amygdala	sgACC	Rest	4 sgACC seeds
Cullen et al. (2009)	12	14	16.6	↓	mPFC, STG, Insula	sgACC	Rest	sgACC, dACC, amygdala seeds
Gabbay et al. (2013)	21	21	16.7	↑	Caudate	sgACC, pgACC	Rest	6 striatal seeds
Geng et al. (2016)	26	31	15.6	–	–	–	Rest	Hippocampus seed
Kim et al. (2016)	22	20	14	–	–	–	Rest	Amygdala, PCC seeds
Pannekoek et al. (2014)	26	26	15	↑ ↓	Amygala mPFC	pgACC dACC	Rest	Amygdala, dACC, PCC seeds
Henje Blom et al. (2015)	31	36	16	↑	Insula	dACC	Viewing affective faces	Insula seed
Ho et al. (2014)	19	19	16	↓ ↑	mPFC, insula, fusiform, precuneus Amygdala	sgACC	Viewing fearful faces	sgACC seed
Ho et al. (2015)	26	37	16	↑	mPFC, PCC	dACC	Viewing affective faces	mPFC, PCC seeds
Kerestes et al. (2016)	29	43	15.3	–	–	–	Viewing Happy Faces	Putamen, dlPFC seeds
Perlman et al. (2012)	14	14	15.4	↑	Amygdala	sgACC	Emotion regulation task	Amygdala seed

Note: Papers are listed by name of first author; et al. is implied. Upward arrow indicates greater value in clinical or high-risk group than in typically developing (TD) group. HR: high-risk; LR: low-risk; FA: fractional anisotropy; MD: major depression; ATR: anterior thalamic radiations; ACC: anterior cingulate cortex; PCC: posterior cingulate cortex; dlPFC: dorsolateral prefrontal cortex; dmPFC: dorsomedial PFC; vmPFC: ventromedial PFC; sgACC: subgenual ACC; mPFC: medial PFC; STG: superior temporal gyrus; dACC: dorsal ACC; pgACC: pregenual ACC.
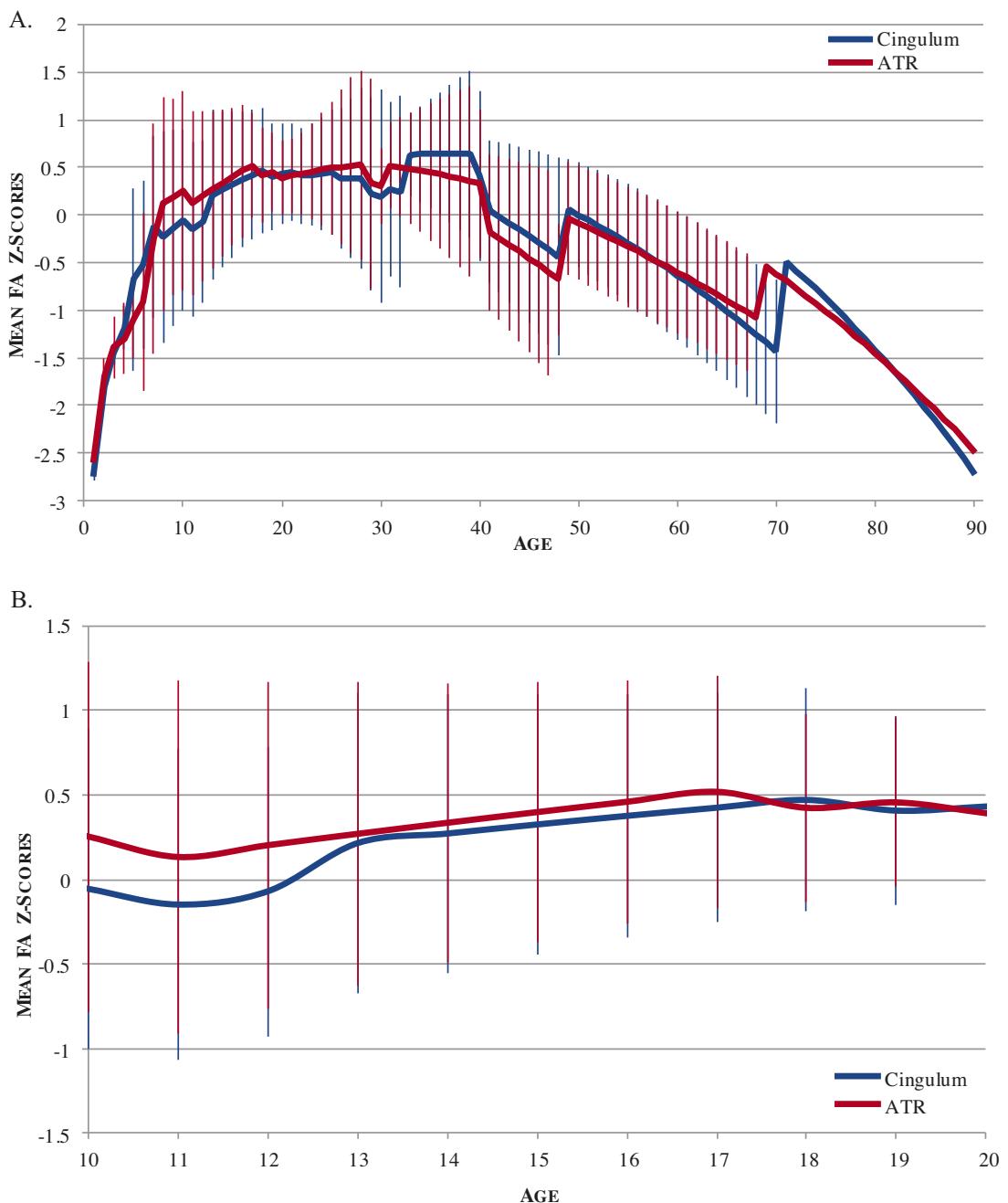
Fig. 3. Developmental trajectories of cingulum and ATR fractional anisotropy. A) Lifetime developmental trajectory of FA from age 0–90. B) Trajectory of FA across adolescence, age 10–20. Lines represent mean FA z-scores from all models included. Because the composite model predictions combine both linear and quadratic effects, both linear and quadratic models are displayed. Error bars depict standard deviations.

existing literature, future studies are necessary to support these hypotheses.

4.1.2. Adolescents with depression

Altered white matter integrity of the cingulum (Cullen et al., 2010; Henderson et al., 2013) and ATR (Henderson et al., 2013; LeWinn et al., 2014) has been reported in adolescents with depression relative to typically developing adolescents. Furthermore, among depressed adolescents, lower cingulum FA has been linked to greater depression severity whereas poorer integrity of the ATR is associated with higher anhedonia, a symptom involving difficulty with motivation for or enjoyment of rewarding experiences and reflecting disruption of reward systems (Henderson et al., 2013). These results support the hypothesis that disrupted development

of structural ACC connectivity is implicated in the emergence of affective problems in adolescence and suggests that white matter integrity of the cingulum and ATR has a significant impact on symptom presentation and illness severity.

4.2. Functional ACC connectivity

Given the available evidence that white matter integrity is distributed in tracts connecting the ACC to various cortical and subcortical regions throughout the brain, functional connectivity of the ACC among depressed adolescents is also likely to deviate from that in typically developing youth. In particular, adolescents with depression are postulated to exhibit disruptions in both affective and cognitive domains—with over-engagement of negative affect
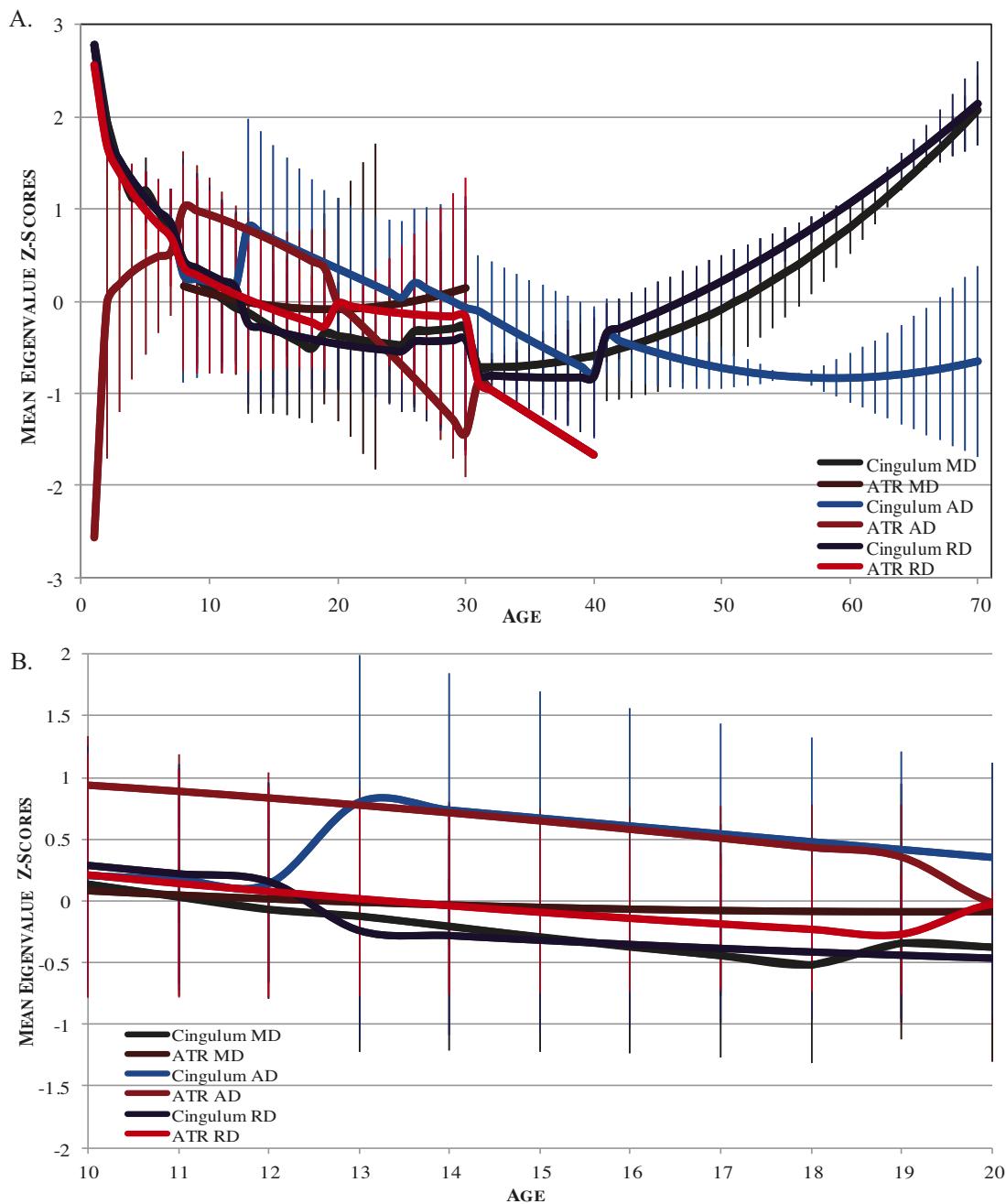
Fig. 4. Developmental trajectories of cingulum and ATR MD, RD, and AD. A) Lifetime developmental trajectory of MD, RD and AD from age 0–70. B) Trajectory of MD, RD, and AD across adolescence, age 10–20. Lines represent mean z-scores for each measure across all models included. Both linear and quadratic effects are displayed. Error bars depict standard deviations. MD: mean diffusivity; AD: axial diffusivity; RD: radial diffusivity.

systems (i.e. sgACC, Phillips et al., 2008), under-engagement of positive affect systems (e.g. Forbes and Dahl, 2012), and ineffective engagement of cognitive or self-regulatory systems (Rayner et al., 2016). Additionally, depressed adults have been reported to show increased activation of the DMN in association with higher levels of rumination compared to healthy adults and hyperactivation of the SN in response to negative stimuli (Hamilton et al., 2013).

4.2.1. Adolescents at high risk for affective disorders

A small number of studies have examined premorbid differences in resting-state connectivity among individuals at high risk for depression based on family history prior to the onset of clinically significant depressive symptoms. These studies provide evidence for premorbid abnormalities in ACC connectivity among high-risk

youth, including greater connectivity between the sgACC and the default mode network, reduced connectivity between the sgACC and the dlPFC (Chai et al., 2015), as well as decreased resting-state connectivity between the dACC and the rostral inferior frontal gyrus relative to those with no family history of depression (Clasen et al., 2014).

4.2.2. Adolescents with depression

Several studies have examined resting-state connectivity among adolescents with current depression and provide preliminary evidence to suggest that these individuals are characterized by aberrant connectivity of the sgACC. Specifically, Cullen et al. (2009) demonstrated decreased resting-state connectivity between the sgACC and distributed frontal cortical regions. Lending additional

support to these findings, Strikwerda-Brown et al. (2015) found that weaker resting-state connectivity between the sgACC and dPFC was associated with higher depressive symptoms in a psychiatrically healthy sample of adolescents, and that decreased connectivity over 2 years predicted increased depressive symptoms over the same follow-up interval. Additionally, there is also evidence to suggest that depressed adolescents display increased resting-state sgACC connectivity with the amygdala (Connolly et al., 2013) and striatum (Gabbay et al., 2013). These data were corroborated by findings that greater sgACC-amygdala connectivity at rest was associated with greater magnitude of negative affect in a sample of healthy adolescents (Davey et al., 2015).

Findings have been relatively more mixed regarding sgACC connectivity to the insula, with both increased (Connolly et al., 2013) and decreased (Cullen et al., 2009) connectivity reported across studies. However, this discrepancy may be due to the fact that one study included adolescents who were listening to music during the resting-state scan (Cullen et al., 2009). Alternatively, resting-state connectivity of the sgACC in depressed adolescents may differ for different subregions of the insula, which have distinct profiles of connectivity and function (Uddin, 2015). Future studies are necessary to clarify the nature and significance of sgACC-insula connectivity in adolescents with depression.

Very few studies have reported aberrant functional connectivity of the dACC and rACC in depressed adolescents. Pannekoek et al. (2014) found decreased connectivity between the dACC and several frontal cortical regions, as well as reduced negative connectivity between the rACC and the bilateral amygdala. Gabbay et al. (2013) reported that greater resting state connectivity between the rACC and the caudate predicted greater anhedonia among depressed adolescents. These studies suggest that aberrant ACC connectivity among depressed adolescents may extend beyond the sgACC, but future studies are necessary to conclusively establish whether these individuals display abnormal patterns of dACC or rACC connectivity at rest.

Studies of task-based functional connectivity are consistent with resting-state findings of higher sgACC-amygdala connectivity among depressed adolescents. During passive viewing of negative stimuli (strongly fearful faces) (Ho et al., 2014), as well as during active affect regulation (cognitive reappraisal of negative images) (Perlman et al., 2012), depressed adolescents display stronger functional connectivity between the sgACC and the amygdala compared to typically developing adolescents. Also in line with the resting-state literature, depressed adolescents show decreased functional connectivity between the sgACC and the middle frontal gyrus, as well as the insula/putamen, fusiform gyrus, and precuneus/posterior cingulate (Ho et al., 2014).

Task-based functional connectivity studies have also shed light on altered dACC connectivity in adolescent depression. Specifically, when adolescents view affectively valenced faces, greater functional connectivity has been reported between the dACC and the mPFC (Ho et al., 2015), as well as the anterior and middle insular cortex (Henje Blom et al., 2015). The latter finding may be indicative of aberrant functioning of the salience network in adolescent depression (Henje Blom et al., 2015), and future research is necessary to assess how salience network functioning may differ between depressed and typically developing adolescents.

4.2.3. Summary of ACC functional connectivity in adolescent affective disorders

Across studies, adolescents with depression exhibit greater functional connectivity between the sgACC and amygdala (Connolly et al., 2013; Davey et al., 2015; Ho et al., 2014; Perlman et al., 2012) coupled with reduced connectivity between sgACC and frontal cortical regions (Cullen et al., 2009; Ho et al., 2014; Strikwerda-Brown et al., 2015) both at rest and during tasks, which

could reflect an overengagement of negative affect systems in tandem with inefficient top-down regulation, resulting in ineffective regulation of affective responding. Furthermore, increased functional connectivity between the dACC and insula during affective processing may contribute to difficulty switching from ruminative and self-referential processing (Henje Blom et al., 2015) and supports the idea that depressed adolescents are characterized by overengagement of the SN to negative stimuli.

4.3. Integration of Structural and Functional ACC Connectivity in Adolescent Depression

In all, both structural and functional connectivity of the ACC appear to be disrupted in adolescent depression. Depressed adolescents display reduced white matter integrity of the cingulum and ATR, as well as stronger sgACC-amygdala connectivity, weaker functional connectivity between the sgACC and frontal cortical regions, and stronger dACC-insula functional connectivity when viewing affective faces. While still preliminary, this literature supports the widespread disruption of ACC connectivity in adolescent depression that is consistent with amplified negative affective reactivity, a bias towards negative stimuli in the environment, and disrupted top-down affect regulation, which may collectively impair goal-directed self-regulatory processes driven by the ACC. Given that alterations in ACC connectivity have been reported in adolescents at high risk for depression prior to illness onset, we hypothesize that aberrant ACC connectivity is a premorbid characteristic that contributes to the onset of MDD. Altered ACC connectivity could be attributable to genetic variation (Braskie et al., 2012), environmental impoverishment (Wang and Young, 2014), or exposure to stress (Howell et al., 2013; Sanjuan et al., 2013) or maltreatment (Choi et al., 2009; Huang et al., 2012) during development. Subsequently, social withdrawal and academic underachievement in the context of active depressive symptoms could exacerbate aberrant patterns of ACC connectivity and contribute to a negative long-term trajectory of mental health and socioeconomic status.

5. Discussion

5.1. Limitations of studies to date

The current review and meta-analysis finds that both structural and functional ACC connectivity develop across adolescence, and proposes that age-related changes in the ACC's structural and functional networks facilitate improved affect regulation and the establishment of adult-level skills necessary to navigate the transition to adulthood. Accordingly, we assert that aberrant ACC connectivity is an important neural mechanism of risk for depression. The literature linking altered structural and functional ACC connectivity to depression in adolescence supports this claim.

Although there has been a recent surge in the number of studies looking at the development of neural network characteristics and their implications for psychopathology, there are several limitations of this literature that must be improved upon in future research. Many studies of white matter development included in the current meta-analysis include small samples, limiting the strength of the conclusions that can be drawn from this data. Additionally, the vast majority of studies use cross-sectional designs, and those reporting longitudinal data include very short follow-up intervals, limiting the strength of the conclusions that can be drawn from this work. Additionally, studies vary in their definitions of adolescence, so the ages of participants included is not consistent. Although adolescence is broadly considered to be the period when individuals transition from dependence on parents to relative

independence (Spear, 2000), the precise onset and offset of adolescence are difficult to delineate. As a result, there are discrepancies between the age ranges included in different studies. Furthermore, the predominance of cross-sectional studies is a significant barrier to understanding whether aberrant ACC connectivity is a stable pre-morbid risk factor, a cause, a concurrent correlate, or a consequence of adolescent psychopathology. Studies that follow larger samples throughout adolescence are necessary to more conclusively delineate typical and maladaptive patterns of ACC development during this period. Additionally, this literature is characterized by substantial methodological heterogeneity, including the magnet strength and imaging parameters applied, analytical methods, and statistical approaches employed across different studies, which significantly limits opportunities for replication between studies.

For functional connectivity findings, interpretation is complicated by the use of rest in some studies and task in others and the use of different types of tasks in task fMRI studies (e.g., cognitive control vs. affective processing). Methodologically, studies used different strategies for computing functional connectivity and, for seed-based functional connectivity, did not consistently select the ACC or a subregion of the ACC as seed. Thus, we interpret the pattern of findings cautiously, given the small number of reports and the differences across them. In terms of both investigations of neural circuitry and methodology for conducting such investigations, the field is changing rapidly. As more developmental and clinical neuroscience studies report their findings, we will have a more comprehensive picture of the connectivity of the ACC as it is disrupted in adolescent depression.

Additionally, there is only a small, heterogeneous literature available on ACC connectivity and adolescent depression. Furthermore, studies that focus on single disorders may be limited in their potential to uncover the neural mechanisms of psychopathology, as psychiatric disorders have heterogeneous symptom presentations and rarely occur in isolation, often co-occurring with other conditions. Indeed, the functions attributed to the ACC and its neural network impact behavior across several domains, and are not specific to one type of psychopathology. Research geared towards elucidating behavioral correlates of ACC function and dysfunction may be more useful for improving our understanding of the role of ACC connectivity relative to studies of discrete clinical populations.

Furthermore, a large proportion of earlier work examining adaptive neural development and risk for psychopathology in adolescence has focused on identifying specific abnormalities in a single brain region or small group of regions. More recently, researchers have come to appreciate that this approach may not be sufficiently complex to further our understanding of brain function in health and disease and there has been a paradigm shift towards studying how brain regions interact across time (Menon, 2011). Nonetheless, this remains a new area of research and substantial future work is necessary to improve our understanding of developing neural network dynamics and their role in adaptive functioning as well as adolescent psychopathology.

5.2. Next steps

Although the current review and meta-analysis provide strong support for the hypothesis that the development of structural ACC connectivity is ongoing throughout adolescence and into young adulthood, substantial future work is necessary to establish the course of microstructural development during the adolescent period and elucidate the cellular basis of these changes. To this end, longitudinal studies with multiple imaging assessments across adolescence are necessary, as well as translational animal studies to relate developmental white matter changes to underlying cellular processes during adolescence. However, consistent with challenges to studying human adolescents, translational research

on adolescent ACC development is complicated by controversy over operationalizing adolescence (Spear, 2015), as well as delineating brain regions that are homologous to the human ACC (Vogt et al., 2013).

Additionally, future research is needed to firmly establish links between structural connectivity, functional connectivity, patterns of neural activation and behavior across typical development and among depressed youth. Powerful recent findings have begun to reveal how anatomical connectivity impacts functional connectivity and patterns of coactivation also modulate the structural integrity of white matter pathways (Luna et al., 2015). However, the mechanisms of these associations remain poorly understood. Future research should address how structural and functional connectivity influence each other and elucidate the time course of these effects as well as potential moderators. Additionally, future work should directly address how improvements in different higher-order functions relate to cingulum and ATR microstructural development and whether functional connectivity mediates these associations.

Furthermore, future research is necessary to elucidate how the maturation of neurotransmitter systems moderates the development of structural and functional ACC connectivity in adolescence. In particular, the dopamine system undergoes substantial alterations during this period, characterized by a shift towards greater cortical dopaminergic innervation in adolescence relative to childhood, when striatal dopaminergic projections are more dominant (see Gomes et al., 2016 for review). Changes in dopaminergic functioning in adolescence are hypothesized to have an important influence on prefrontal cortical synaptic plasticity and myelination (Davey et al., 2008), suggesting that dopamine system changes may meaningfully impact the development of cingulum and ATR microstructure as well as functional ACC connectivity.

Another crucial step is to examine network-to-network functional connectivity. Because the brain comprises a set of interdependent networks that require coordination across and within networks to guide adaptive behavior (Dosenbach et al., 2008; Luna et al., 2015), it is important to move beyond a single-network emphasis. With the field of developmental connectomics gaining momentum (Hagmann et al., 2012), more studies are taking this approach. Recent relevant investigations have addressed alterations in the balance of network function in, for example, adolescent depression (Jacobs et al., 2014) and other psychopathology (e.g. Wang et al., 2016).

The guiding conceptual model of current research in psychopathology is that this construct is captured perhaps more appropriately in a set of dimensions related to affect, cognition, and behavior rather than in a set of diagnostic categories based on phenomenology and self-report. As approaches such as NIMH's Research Domain Criteria (aka RDoC; https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml) initiative increasingly influence the operationalization of psychopathology and developmental psychopathology approaches gain prominence, we will see more research addressing a range of important but underappreciated issues. From an RDoC-style or dimensional perspective, these issues include common, transdiagnostic factors (e.g., P or general psychopathology, Caspi et al., 2014); dimensions related to multiple forms of psychopathology (e.g., reward or "positive valence system" disruption); and multi-method approaches to operationalizing these dimensions. From a developmental psychopathology perspective, these issues include longitudinal designs, examining atypical development in the context of typical development, and modeling within-person trajectories to understand the unfolding of psychopathology over time. An invaluable tool in this progress will be the application of sophisticated data analytic methods combined with large data sets, possibly promoted through data sharing. We expect to see more studies using functional and structural con-

nectivity of the ACC or other central regions as predictors in large multi-method models of adolescent psychopathology, similar to what has been done in recent papers on alcohol use in the large, multi-site IMAGEN study of adolescent development (Nees et al., 2012; Whelan et al., 2014).

We are limited to describing the literature using samples from studies using discrete, DSM-defined groups and employing case-control designs because that approach has been the norm for developmental psychopathology and clinical neuroscience research. But soon we hope that we will be able to write a similar conceptual paper by citing a literature that is more diverse, generalizable, and developmentally informed in order to more appropriately capture the mechanisms of developmental psychopathology.

Finally, while not directly applicable to treatment or prevention efforts, we argue that research on the neuroscience of developmental psychopathology should have clinical relevance. Whether applied to evaluating the influence of standard treatments on changes in functional connectivity in depression, as in the case of pharmacologic treatment for depression (Gudayol-Ferre et al., 2015), using brain function to predict the outcome or mechanisms of effective treatments such as electroconvulsive therapy (Perrin et al., 2012; van Waarde et al., 2015), or examining the mechanistic targets for novel brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS, Baeken et al., 2014), understanding connectivity in neural networks can generate progress in therapeutics. Not surprisingly, given its importance to developmental psychopathology, connectivity of the ACC has been implicated in each of these research directions for depression (e.g. Barrett et al., 2004; Leaver et al., 2016; Spati et al., 2015). Research in this field could also, ultimately, identify new brain targets for intervention. While some have expressed despair about the future of treatment for psychopathology (Hyman, 2014), a path toward alleviating suffering should surely include greater attention to the development of serious psychopathology through a more comprehensive understanding of brain development.

5.3. Conclusions

In all, connectivity of the ACC is important to typical adolescent development and risk for adolescent depression. This is consistent with our guiding hypothesis: development of the ACC and associated self regulatory abilities are a key process of adolescent developmental psychopathology. Structural and functional connectivity of the ACC develop during adolescence, as indicated by our meta-analytic findings on structure and review of the literature on function. Furthermore, altered patterns of both structural and functional connectivity have been observed among adolescents at high risk for mood disorders and those with current depression. The field still has considerable opportunity for studies of structure-function association, prospective developmental studies of psychopathology, and studies examining brain structure and function as part of a complex set of mechanisms and risk factors. Furthermore, future research is needed to examine the influence of ACC development on risk for other forms of adolescent psychopathology, such as anxiety, bipolar disorder and substance use disorder. The current review provides a valuable step toward understanding the developmental psychopathology and developmental neuroscience of adolescence.

Acknowledgments

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