A review of default mode network connectivity and its association with social cognition in adolescents with autism spectrum disorder and early-onset psychosis

Aarti Nair[1], Morgan Jolliffe[2], Yong Seuk S. Lograsso[1,3], Carrie E. Bearden[1,4]

[1]Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, UCLA

[2]Graduate School of Professional Psychology, University of Denver

[3]Division of the Humanities and Social Sciences, California Institute of Technology

[4] Department of Psychology, UCLA

Correspondence:

Corresponding Author: Aarti Nair, Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, UCLA

660 Charles E Young Drive South, Suite 209, Los Angeles, CA 90095

Tel.: 310-794-4024

Email: anair@mednet.ucla.edu

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Abstract

Recent studies have demonstrated substantial phenotypic overlap, notably social impairment, between autism spectrum disorder (ASD) and schizophrenia. However, the neural mechanisms underlying the pathogenesis of social impairments across these distinct neuropsychiatric disorders has not yet been fully examined. Most neuroimaging studies to date have focused on adults with these disorders, with little known about the neural underpinnings of social impairments in younger populations. Here, we review the literature available through March 2020 on imaging studies of adolescents with either ASD or early-onset psychosis (EOP), to better understand the shared and unique neural mechanisms of social difficulties across diagnosis from a developmental framework. We specifically focus on functional connectivity studies of the default mode network (DMN), as the most extensively studied brain network relevant to social cognition across both groups. Our review included 29 studies of DMN connectivity in adolescents with ASD (Mean age range = 11.2-21.6 years), and 14 studies in adolescents with EOP (Mean age range = 14.2-24.3 years). Of these, 15 of 29 studies in ASD adolescents found predominant underconnectivity when examining DMN connectivity. In contrast, findings were mixed in adolescents with EOP, with five of 14 studies reporting DMN underconnectivity, and an additional six of 14 studies reporting both under- and over-connectivity of the DMN. Specifically, intra-DMN networks were more frequently underconnected in ASD, but overconnected in EOP. On the other hand, inter-DMN connectivity patterns were mixed (both under- and over-connected) for each group, especially DMN connectivity with frontal, sensorimotor, and temporoparietal regions in ASD, and with frontal, temporal, subcortical, and cerebellar regions in EOP. Finally, disrupted DMN connectivity appeared to be associated with social impairments in both groups, less so with other features distinct to each condition, such as repetitive behaviors/restricted interests in ASD and hallucinations/ delusions in EOP. Further studies on demographically well-matched groups of adolescents with each of these conditions are needed to systematically explore additional critical contributing factors in DMN connectivity patterns such as clinical heterogeneity, pubertal development, and medication effects that would better inform treatment targets and facilitate prediction of social outcomes in the context of these developmental neuropsychiatric conditions.

47 Keywords: functional connectivity, default mode network, social cognition, autism spectrum
48 disorder, early-onset psychosis

Introduction

Autism spectrum disorder (ASD) and schizophrenia are heterogeneous conditions that share several phenotypic and genomic features (Crespi and Badcock, 2008; Rapoport et al., 2009; Stone and Iguchi, 2011; Chisholm et al., 2015). For instance, deficits in social interaction, emotional reciprocity, pragmatic speech, and theory of mind (ToM) are postulated to be central to both disorders (Chung et al., 2014). While early detection and clinical diagnosis of both disorders has improved over the past decade, frequent challenges still arise in differential diagnosis (e.g., in the event of later diagnosis of ASD) especially if predominant symptoms for both involve social difficulties and unusual social thinking (Dossetor, 2007; Rapoport et al., 2009). Recent behavioral studies of adults with ASD and schizophrenia highlighted not only the similarities but also some divergent patterns of social impairments in the two disorders – with ASD characterized by lower social motivation, poorer social reciprocity, and undermentalizing, and schizophrenia characterized by greater reciprocity but poor expressiveness (Morrison et al., 2017; Pepper et al., 2018). Moreover, these social impairments are associated with difficulties in the work setting (Marwaha and Johnson, 2004; Taylor et al., 2015), social relationships (Howlin et al., 2004; Horan et al., 2006), and overall reduced quality of life (Eack et al., 2007; Barneveld et al., 2014) across both groups. While several studies have demonstrated genetic overlap between ASD and schizophrenia (Rapoport et al., 2009; Stone and Iguchi, 2011; Chisholm et al., 2015; O'Connell et al., 2018), the neural mechanisms underlying the pathogenesis of the social impairments observed in these disorders are still not well understood. Given the public health significance of social disability and social isolation (Green, 2017), it is crucial to explore the neurobiological mechanisms underlying social deficits across both groups, as well as to understand how they relate to real-world behaviors. Exploring the shared and distinct neural underpinnings in ASD and schizophrenia could advance our understanding of social cognitive deficits across these conditions, which will ultimately help better inform treatment. Although antipsychotics have been shown to be effective in reducing positive symptoms in schizophrenia, they are not effective in addressing the devastating social disability associated with the disorder which contributes to chronic functional impairment (Owen et al., 2016; Horan and Green, 2017). It is thus imperative to identify behavioral interventions for children and adolescents that have already shown promise in other clinical groups such as ASD. By enhancing our understanding of the neurobiological underpinnings of social impairments in ASD and how they compare to those

observed in schizophrenia, we will be able to refine treatment targets and predict outcomes for each group.

Adolescence is a particularly critical window for social development and thus is an important time to investigate neural mechanisms implicated in social functioning. Adolescence is a developmental period classified by gaining independence and autonomy from caretakers (Casey et al., 2011), with marked changes in identity, self-consciousness, and cognitive flexibility (Rutter, 1993; Blakemore and Choudhury, 2006; Happe and Frith, 2014). As a part of this process of developing as an independent individual, there is typically an increase in peer-directed social interactions (Blakemore and Choudhury, 2006; Blakemore, 2008; Casey et al., 2011). As a result of this increase in sociality, adolescence is a time when the social demands change most dramatically, requiring individuals with social deficits to work harder. Prior research has shown that social deficits become even more apparent during this period as social contexts increase in complexity and pose higher social expectations (White, 2007; Happe and Frith, 2014). Consequences of poor social skills include peer rejection or victimization, poor friendship quality, lack of social support, experiences of loneliness, poor academic and vocational outcomes, and the development of anxiety, depression, or other psychopathologies (Bauminger and Kasari, 2000; Chamberlain et al., 2007; Rao et al., 2008). For individuals with ASD, adolescence may be a particularly difficult developmental period as they are also experiencing increased motivation to engage with peers, yet likely have a greater awareness of their social deficits (Tantam, 2003). For individuals with psychotic disorder, negative symptoms including social withdrawal, reduced communication, and general apathy often precede positive symptoms and are linked more strongly to poor prognosis (Hooley, 2010; Carrion et al., 2016; Addington et al., 2017; Kaneko, 2018). The fact that social deficits often precede full-blown positive symptoms in schizophrenia implies that there are likely neural changes occurring during adolescence that precede manifestation of psychotic symptoms in early adulthood. While social impairment is a hallmark of both ASD and psychosis, these difficulties may have distinct origins: for example, the hypo-hyper-intentionality hypothesis (Abu-Akel et al., 2000; Crespi and Badcock, 2008) postulates that individuals with ASD may under-attribute intentions to others or "undermentalize", whereas those with schizophrenia may over-attribute intentions to others or "overmentalize", parlaying into symptoms of suspiciousness and paranoia.

In addition to contextual changes in the social environment, adolescence is also a period marked by significant neural changes, particularly in the prefrontal cortex, a major hub in several brain networks associated with social functioning (Blakemore and Choudhury, 2006; Fair et al., 2008; Power et al., 2010; Sturman and Moghaddam, 2011; Klapwijk et al., 2013; Keshavan et al., 2014; Sole-Padulles et al., 2016). Evidence suggests that while sensory and motor brain regions are fully myelinated within the first several years of an infants' life, neurons in the frontal cortex continue to be myelinated through adolescence (Blakemore and Choudhury, 2006; Casey et al., 2011; Keshavan et al., 2014). This increased myelination as well as white matter density is coupled with decreases in cortical thickness and gray matter in social brain hubs in frontal and parietal lobes (Sturman and Moghaddam, 2011; Keshavan et al., 2014). Additionally, synaptic pruning – the process of eliminating unused neural connections, and the reorganization of strengthened pathways – is occurring actively in the prefrontal cortex during puberty (Bourgeois et al., 1994; Rakic et al., 1994; Zecevic and Rakic, 2001; Blakemore and Choudhury, 2006; Blakemore, 2008). As a result, adolescents experience a net decrease in synaptic density during this time (Blakemore & Choudhury, 2006) along with increased long-distance and decreased short-distance functional connections in the brain, indexing better network integration and segregation during this period (Rubia, 2013; Hulvershorn et al., 2014). Increases in functional activation of prefrontal cortex are also observed in typical adolescents compared to adults in response to social tasks (Blakemore, 2008; Sturman and Moghaddam, 2011). Increased functional connectivity between prefrontal cortex and temporal brain regions during adolescence is also related to increased social information processing during this age (Klapwijk et al., 2013). Other studies have suggested that brain regions involved in social information processing demonstrate strengthening of connectivity from childhood to late adolescence (Fair et al., 2008; Power et al., 2010; Rubia, 2013; Sole-Padulles et al., 2016).

Although the social brain is not a specifically defined network, there is general consensus in the literature that the medial prefrontal regions, the temporoparietal junction, anterior and lateral temporal regions, anterior insula and the posterior cingulate cortex/precuneus subserve several crucial social functions (Blakemore, 2008; Kennedy and Adolphs, 2012; Keshavan et al., 2014). Of note, the aforementioned brain regions are all highly represented within the default mode network (DMN) – a large-scale brain network with hubs in the medial prefrontal cortex (mPFC), posterior cingulate cortex/precuneus (PCC), inferior parietal lobe (IPL), and temporal lobe

structures (Raichle et al., 2001; Fox et al., 2005; Buckner et al., 2008). The DMN is one of the most extensively studied functional networks, and it shows substantial overlap with several other 'social brain' networks such as the mentalizing network and emotion recognition network (Kennedy and Adolphs, 2012; Mars et al., 2012; Li et al., 2014). It has been proposed that the DMN is specifically involved in self-referential thinking (Gusnard et al., 2001a; Gusnard et al., 2001b; Andrews-Hanna et al., 2010; Andrews-Hanna et al., 2014), thoughts about self versus others and theory of mind (Buckner et al., 2008; Schilbach et al., 2008; Lombardo et al., 2010; Li et al., 2014), and autobiographical memory (Andrews-Hanna et al., 2010; Andrews-Hanna et al., 2014). As such, disrupted DMN functional connectivity has been implicated in several psychiatric conditions with associated social difficulties (Menon, 2011; Kennedy and Adolphs, 2012; Whitfield-Gabrieli and Ford, 2012; Philippi and Koenigs, 2014), including ASD (Padmanabhan et al., 2017) and schizophrenia (Hu et al., 2017). With such a rich literature, investigation of DMN function in adolescence offers a window into understanding how these social brain regions are functionally connected, how they are altered in disorders affecting social function, and their relationship to real-world social deficits.

Much of this existing literature on the social brain and DMN connectivity has, however, focused on children (for ASD) and adults (for schizophrenia/psychosis), with fewer studies focusing on adolescents. While ASD may be diagnosed earlier in life, there is evidence to suggest that functional connectivity patterns in individuals with this condition undergo substantial changes from childhood to adulthood, likely influenced by factors such as puberty and/or access to treatment interventions over the years (Uddin et al., 2013). In contrast, the age of onset for psychotic disorder peaks in adolescence, but more subtle cognitive and socio-emotional disturbances are present in early childhood (Cannon et al., 2003). It is posited that overt symptom onset of psychosis during adolescence may be related to underlying changes in brain connectivity patterns affected by hormonal changes and increased stress response during this period (Keshavan et al., 2014). Due to the importance of this developmental period for brain development in general, as well as the relevant changes to social contexts, examining brain networks implicated with social cognition such as the DMN in adolescence requires substantial attention to further our understanding of the shared and distinct neural mechanisms underlying the social cognition deficits present in each group.

Hence, the current article aims to further explore cross-sectional studies on DMN connectivity in ASD and early-onset psychosis (EOP) during the adolescent years. For this purpose, we reviewed the literature available through March 2020 in PubMed, Google Scholar, and PsycINFO on DMN connectivity in adolescents with ASD and/or EOP, using search terms including "default mode network, functional connectivity," combined with "adolescence, autism, ASD, Asperger's" or "psychosis, adolescent-onset psychosis, adolescent-onset schizophrenia, first-episode psychosis, early-onset psychosis, early-onset schizophrenia". The initial literature search revealed 160 relevant studies in ASD and 46 in EOP. Studies were subsequently included in the review based on age-range spanning adolescence and patient groups meeting diagnostic criteria for either ASD or EOP. All included studies were also required to have a control group of typically developing adolescents. Additionally, we focused only on empirical studies that included either: 1) static resting-state analysis or dynamic functional connectivity (DFC) analysis that examines temporal variations in connectivity patterns across the duration of the scan (Chang and Glover, 2010; Allen et al., 2014; Hutchison and Everling, 2014), and 2) provided information about the directionality of their findings. The methods used for these studies included:

1) Traditional seed-based analysis, wherein the time-series from a seed-region are correlated with all other voxels in the entire brain or a mask of the DMN (Biswal et al., 1995; Smitha et al., 2017).
2) Seed-based analyses that quantify the amplitude of low-frequency fluctuations (ALFF), i.e., the magnitude of signal intensity of spontaneous fluctuations for a given brain region. In ALFF analyses, the time-series from a given seed-region are transformed into a frequency domain from which the power spectrum are obtained (Zang et al., 2007; Smitha et al., 2017).
3) Independent component analyses (ICA), a data-driven method wherein whole-brain signal are decomposed to identify spatially and temporally independent components. Software templates of the DMN are then used to identify components that correspond to this network (Smitha et al., 2017).
4) Support vector machines (SVM) are data-driven supervised machine-learning methods using pattern recognition algorithms to automatically classify neuroimaging data into typical or atypical categories (Chaplot, 2006).

5) Self-organizing map (SOM) algorithm, a clustering analysis technique wherein voxels are organized on a two-dimensional matrix with each node representing clusters of voxels that are highly correlated and nodes that are closer together on matrix representing neural networks (Chaplot, 2006; Wiggins et al., 2011).
6) Regional Homogeneity (ReHo), a voxel-based approach to measuring brain connectivity wherein the similarity between the time-series of a given voxel and its nearest neighbors within a network is evaluated (Zang et al., 2004).
7) Granger Causality Analysis (GCA), a statistical method that allows for prediction of causality between functional connectivity of two seed-regions/nodes from time-series data (Seth et al., 2015).
8) Network Homogeneity (NH), a voxel-wise measurement of homogeneity and cohesiveness of each voxel within a functional network that provides an index of network integrity (Uddin et al., 2008).

Our final review included 29 studies of DMN connectivity in adolescents with ASD (mean age range = 11.2-21.6 years; see Table 1 for demographic details), and 14 studies in adolescents with EOP (Mean age range = 14.2-24.3 years; see Table 3 for demographic details). Our goal is to synthesize the findings of altered DMN connectivity from the existing literature for each clinical population within a developmental framework, and discuss how the potential commonalities or differences in underlying neural mechanisms may relate to characteristic symptomatology. We conclude by providing some insights into gaps within the extant literature and highlighting future directions for research.

DMN connectivity in adolescents with ASD

The past few years have witnessed a proliferation of resting-state connectivity studies in adolescents with ASD, facilitated in part by the availability of open-access multinational datasets such as the Autism Brain Imaging Data Exchange (ABIDE; Di Martino et al., 2014). Approximately 52% of the studies in adolescents with ASD presented in our review (Table 1 and 2) have utilized the ABIDE dataset to investigate DMN connectivity (Nielsen et al., 2014; Nomi and Uddin, 2015; Elton et al., 2016; Falahpour et al., 2016; Ypma et al., 2016; Chen et al., 2017; Duan et al., 2017; Guo et al., 2017; Bi et al., 2018; Kernbach et al., 2018; Borras-Ferris et al., 2019; Guo et al., 2019; Lawrence et al., 2019; Reiter et al., 2019; Wang et al., 2019a). About half

of the studies (15 out of 29) in adolescents with ASD have found a global pattern of underconnectivity both within the DMN hubs (Assaf et al., 2010; Weng et al., 2010; Starck et al., 2013; Falahpour et al., 2016; Ypma et al., 2016; Duan et al., 2017; Neufeld et al., 2018; Borras-Ferris et al., 2019; Reiter et al., 2019), as well as between the DMN and other brain regions such as insula, subcortical regions, fronto-parietal regions, and visual cortex (Wiggins et al., 2011; Nielsen et al., 2014; Nomi and Uddin, 2015; Duan et al., 2017; Kernbach et al., 2018; Guo et al., 2019), regardless of analytic methods used. Relatively fewer studies (five out of 29) have observed over-connectivity between the DMN and task-positive regions within the fronto-parietal, visual, and sensorimotor regions, as well as the salience network (Redcay et al., 2013; Elton et al., 2016; Hogeveen et al., 2018; Gao et al., 2019; Mash et al., 2019). Some studies (nine out of 29) have additionally found mixed patterns involving under- and over-connectivity of ASD youth relative to typically developing (TD) controls, largely highlighting a pattern of within-DMN underconnectivity, with overconnectivity between DMN and other networks such as task-positive or sensorimotor networks (Doyle-Thomas et al., 2015; Jann et al., 2015; Abbott et al., 2016; Chen et al., 2017; Guo et al., 2017; Joshi et al., 2017; Bi et al., 2018; Pereira et al., 2018; Lawrence et al., 2019; Wang et al., 2019a). This mixed pattern of connectivity may suggest poor integration within the DMN, along with atypical segregation between the DMN and other related cognitive networks in adolescents with ASD (see Table 2 for main results from each study).

Additional perspectives on DMN connectivity in ASD have been offered by new and emerging studies investigating whole brain DFC. While some of these studies have found broader temporal variability of DMN connectivity across states in adolescents with ASD (Falahpour et al., 2016; Mash et al., 2019), others show predominant patterns of underconnectivity between the DMN and salience, attentional, and visual networks, which is state-dependent and may be related to social cognition states (Duan et al., 2017; Guo et al., 2019). Since DFC is a relatively new realm of functional connectivity research, additional investigations of dynamic DMN connectivity as it relates to adolescents with ASD is warranted to further delineate such state-dependent patterns. In addition to static versus dynamic models, one study also examined lateralization of the DMN and its relationship to language networks in adolescents with ASD (Nielsen et al., 2014), and found that the ASD group had significantly less left lateralization of these networks compared to TD controls, suggesting that these language and

social cognition networks may not be as functionally specialized in ASD. They additionally found that this reduced left-lateralization was associated with higher ASD symptom severity.

A few studies have also explored the maturational trajectory of DMN connectivity in individuals with ASD (Wiggins et al., 2011; Nomi and Uddin, 2015; Lawrence et al., 2019). Wiggins et al. (2011) looked at age-related patterns of DMN connectivity cross-sectionally, and found that the ASD group did not demonstrate typical age-related increases in connectivity between the precuneus/PCC hub of the DMN and frontal regions. Nomi et al. (2015) further looked at differences in DMN connectivity between children and adolescents with ASD cross-sectionally, and found that children with ASD showed a pattern of within-DMN overconnectivity and between-network DMN underconnectivity relative to controls. Comparatively, adolescents with ASD did not differ from age-matched controls in within-DMN connectivity but demonstrated underconnectivity between DMN and the salience network and subcortical regions. In a longitudinal study, Lawrence et al. (2019) looked at changes in DMN connectivity between ASD and TD controls from early to late adolescence, and found that TD controls had an age-associated increase in *negative* functional connectivity between the DMN and the task-positive central executive network, not observed in adolescents with ASD. These findings support the theory of a crucial maturational shift in DMN connectivity patterns during adolescence which is likely significantly impacted in individuals with ASD such that the typically expected strengthening and honing of DMN connectivity is disrupted in this population during this age period. However, the mechanism underlying the shift in DMN connectivity patterns after the onset of puberty is not fully understood in ASD yet, and requires further exploration to elucidate differential trajectories and their impact on symptomatology.

So far only one study has systematically examined sex differences in DMN connectivity in ASD (Ypma et al., 2016). This study spanned a wide age range from childhood to adulthood, but in the adolescent subset female TD controls demonstrated stronger within-DMN connectivity relative to male TD controls; comparatively, ASD females and males showed similar within-DMN connectivity strength, that in turn was significantly lower than their TD counterparts. Notably, this DMN hypoconnectivity appeared to be an endophenotype, as it was also observed in the unaffected siblings of ASD cases, relative to TD controls. These findings suggest aberrant DMN connectivity may underlie a broader continuum of autism-relevant traits in the general population.

Intellectual functioning is another variable of interest relevant to DMN connectivity in adolescents with ASD, given the wide range of cognitive abilities in this population (DSM-V, 2013). Most of the studies included in this review focused on adolescents within the normative intellectual functioning range; however, one recent study (Mash et al., 2018) examined the differences in within-DMN connectivity between low (Mean IQ=77±6) and high-IQ ASD participants (Mean IQ=123±8) and found that the low cognitive functioning group demonstrated significant within-DMN underconnectivity compared to the high-functioning group, even after controlling for symptom severity.

Lastly, several of the studies (12 out of 29) included in our review have examined the relationship between aberrant DMN connectivity in adolescents with ASD and behavioral measures of symptom severity such as the Autism Diagnostic Observation Schedule (ADOS; Lord, 1999; 2012), the Autism Diagnostic Interview-Revised (ADI-R; Rutter, 2003), and the Social Responsiveness Scale (SRS; Constantino, 2005; 2012). Studies looking at the association of within-DMN network connectivity with behavioral measures of symptom severity (N=6 studies) found mixed effects, with most (five out of six studies) reporting greater within-DMN network underconnectivity associated with higher social impairment scores on the ADOS (Assaf et al., 2010; Duan et al., 2017;), ADI-R (Weng et al., 2010; Wang et al., 2019a), and SRS (Assaf et al., 2010); while one of the six found greater within-DMN overconnectivity to be associated with higher social impairment scores on the SRS (Jann et al., 2015), and one (using the ADOS) reporting a mixed pattern (Guo et al., 2017) . Studies looking at the association of DMN between-network connectivity with behavioral measures of symptom severity (N=7) mostly found that greater overconnectivity between DMN and other brain regions (mostly in the frontal and temporal lobes; four out of seven studies) was associated with higher social impairments on the ADOS (Chen et al., 2017), ADI-R (trend level; (Pereira et al., 2018), and SRS (Abbott et al., 2016; Elton et al., 2016). Interestingly, in one of the first studies to report DMN overconnectivity in adolescents with ASD, Redcay et al. (2013) found that greater DMN overconnectivity with the right lateral parietal region was associated with less impairment on the social-communication domain of the ADOS, suggesting the possibility of an underlying compensatory mechanism in this particular brain network. Only two out of seven studies looking at the association of DMN between-network connectivity with behavioral measures of symptom severity found that greater underconnectivity between DMN hubs and other brain regions (salience, attention networks) in

ASD was associated with higher symptom severity on the ADOS (Duan et al., 2017; Guo et al., 2019). Additionally, Doyle-Thomas et al. (2015) and Ypma et al. (2016) found that anomalous DMN connectivity patterns in adolescents with ASD (mixed within-DMN connectivity results in the former study, and within-DMN underconnectivity in the latter study) were associated with poorer performance on the "Reading the Mind in the Eyes" Test (RMET; Baron-Cohen et al., 2001), a measure of theory of mind (ToM) and social cognition. Of the studies (all 12 reporting associations between DMN connectivity and behavioral measures of symptom severity) that looked at both the social interaction domain and the repetitive behaviors/restricted interests domain of the ADOS-2 and ADI-R (Assaf et al., 2010; Weng et al., 2010; Redcay et al., 2013; Jann et al., 2015; Abbott et al., 2016; Elton et al., 2016; Chen et al., 2017; Duan et al., 2017; Guo et al., 2017; Pereira et al., 2018; Guo et al., 2019; Wang et al., 2019a), only one study (Weng et al., 2010) reported a significant relationship for DMN within-network underconnectivity patterns and measures of repetitive behaviors/ restricted interests (ADI-R) in ASD adolescents. Hence, it appears that aberrant DMN connectivity may play a larger role in the social functioning deficits experienced by this population rather than other features of ASD.

DMN connectivity in adolescents with EOP

Prior research on adults with schizophrenia spectrum disorders suggests that disrupted DMN connectivity may play an important role in the pathophysiology of schizophrenia (Hu et al., 2017). Specifically, findings in adults with schizophrenia frequently include within-DMN overconnectivity, as well as mixed findings of under- and over-connectivity between DMN and task-positive networks; in turn, these disruptions have been associated with positive symptoms, poor social functioning, as well as poor cognitive functioning in schizophrenia (Hu et al., 2017). Additionally, DMN connectivity has been found to become more 'normative' in response to anti-psychotic treatment in adults with schizophrenia (Sambataro et al., 2010; Surguladze et al., 2011). Some of the inconsistencies found in the literature on DMN connectivity patterns in schizophrenia, with both under- and over-connectivity involving this network being associated with symptom severity, as well as social and cognitive functioning, could be attributed to the heterogeneity of patient characteristics within schizophrenia spectrum disorders. For instance, studies thus far have included individuals with first-episode schizophrenia, chronic patients, drug-naïve patients, as well as patients treated with antipsychotic medications which may have

impacted the results across these studies. Hence, how disease progression as well as treatment status impacts DMN connectivity and its relationship with behavioral outcomes in schizophrenia is not yet clear.

More recent studies of DMN connectivity in adolescents with EOP offer some insight into neural anomalies in the earlier stages of this disorder (Tables 3 and 4). Several EOP studies (11 out of 14) have focused on drug-naïve adolescent patients with psychotic disorder with illness onset within two years (Zhang et al., 2015; Wang et al., 2016; Zheng et al., 2016; Chen et al., 2017; Wang et al., 2017a; Liu et al., 2018; Wang et al., 2018a; Wang et al., 2018b; Zhao et al., 2018; Wang et al., 2019b; Zhang et al., 2020). Of these, the majority (eight out of 11) appear to report on the same (or at least, largely overlapping) cohort (Zhang et al., 2015; Zheng et al., 2016; Wang et al., 2017a; Liu et al., 2018; Wang et al., 2018a; Wang et al., 2018b; Wang et al., 2019b; Zhang et al., 2020). Other EOP studies (three out of 14) have involved independent cohorts of adolescents with recent-onset psychotic disorder receiving anti-psychotic treatment (Tang et al., 2013; Cui et al., 2017; Ilzarbe et al., 2019). Collectively, results suggest a mixed pattern of under- and over-connectivity involving the DMN, similar to that observed in adults with schizophrenia (Hu et al., 2017) and regardless of analytic method or cohort used (see Table 4 for main results from each study).

One study comparing adolescents at clinical high risk for psychosis (CHR) to drug-naïve adolescents with a diagnosed psychotic disorder suggested that while both groups showed increased connectivity between DMN and cerebellum compared to TD control groups, the connectivity strength was attenuated in those with overt illness (Wang et al., 2016). On the other hand, some studies of drug-naïve adolescents with psychotic disorder have reported underconnectivity within the DMN (Zheng et al., 2016; Wang et al., 2017a; Liu et al., 2018) relative to healthy controls, and between DMN and other brain areas such as prefrontal cortex, temporal gyrus, parietal cortex, and limbic regions (Zhang et al., 2015). However, six out of 14 studies investigating DMN connectivity in youth with EOP indicate a mixed pattern of connectivity, both within the DMN as well as between the DMN and other brain regions such as temporal lobe, subcortical regions, and cerebellum (Chen et al., 2017; Wang et al., 2018a; Wang et al., 2018b; Zhao et al., 2018; Wang et al., 2019b; Zhang et al., 2020). One interesting perspective offered by Wang et al. (2018a) from their examination of short versus long-range DMN connectivity is that there is potentially a pattern of overconnectivity involving the anterior

hubs of the DMN, compared to underconnectivity involving the posterior hubs of the DMN in drug-naïve adolescents with psychotic disorder. This perspective is further supported by recent findings of higher network homogeneity in anterior hubs of the DMN but lower in posterior hubs of the DMN in drug-naïve adolescents with psychotic disorder compared to controls (Zhang et al., 2020). In the past few years, studies investigating whole-brain DFC in adolescents with EOP have also emerged (Wang et al., 2017a; Wang et al., 2019b). These studies have been largely consistent with the mixed connectivity findings of the DMN for drug-naïve adolescents with a diagnosed psychotic disorder (Wang et al., 2017a; Wang et al., 2019b) and suggested that over- or under-connectivity of the DMN could be state-dependent, with the precuneus hub of the DMN especially demonstrating differential state-dependent connectivity patterns with other brain regions.

Studies of youth with EOP receiving anti-psychotic medication mostly showed overconnectivity relative to healthy controls within the DMN (Tang et al., 2013; Cui et al., 2017), as well as increased co-activation between DMN and prefrontal cognitive control regions (Cui et al., 2017) with only one study reporting underconnectivity within the DMN (Ilzarbe et al., 2019). It is therefore tempting to speculate that prior to the introduction of anti-psychotic medication the DMN tends to be underconnected or mixed in its connectivity patterns, with changes occurring in the pattern of connectivity after implementation of a medication regimen or as the course of the disease progresses.

Current symptom severity may also impact DMN connectivity patterns in adolescents with EOP. Ten out of 14 studies reviewed here examined the relationship between DMN connectivity and symptom severity on the Positive and Negative Syndrome Scale (PANSS), a widely used measure in schizophrenia (Kay et al., 1987). Out of these, four studies did not find any significant associations between DMN connectivity patterns and PANSS scores (Chen et al., 2017; Wang et al., 2018a; Ilzarbe et al., 2019; Wang et al., 2019b). However, results from six out of 10 studies that found significant relationships between DMN connectivity and the PANSS revealed that aberrant within-DMN connectivity (Tang et al., 2013; Zheng et al., 2016; Wang et al., 2017a) as well as disrupted connectivity between DMN and other brain regions (Zhang et al., 2015; Wang et al., 2016; Zhao et al., 2018) in EOP tended to be more strongly associated with PANSS negative symptoms scores rather than positive symptom scores. Lastly, one recent study found that within-DMN underconnectivity accounted for ~16% of the variance in ToM

performance measured by the RMET in adolescents with EOP treated with anti-psychotics (Ilzarbe et al., 2019). This suggests that the DMN may have a more crucial role in the social impairments observed in adolescents with EOP, rather than positive symptoms such as unusual thought content or perceptual disturbances.

Shared and distinct DMN connectivity patterns in adolescents with ASD and EOP

The only currently published study that has directly compared whole-brain connectivity patterns in adolescents with ASD and EOP (Chen et al., 2017) found that ASD and EOP youth shared a common pattern of disrupted connectivity compared to TD controls, mainly involving the prefrontal nodes of the DMN and salience networks, which is also implicated in social functioning (Di Martino et al., 2009; Rosen et al., 2018). In contrast, they found that disrupted connectivity *between* DMN and salience network was more characteristic of EOP, whereas in ASD the atypical connections were primarily found *within* the salience network. Taken together, the findings reviewed here highlight that ASD and EOP have some convergent, as well as divergent, patterns of dysregulation of DMN networks. Figure 1 provides a schematic representation of findings from all the studies for each group, with yellow dots representing the DMN hub regions, red (underconnected) or blue (overconnected) dots representing connectivity with other brain regions, and thickness of lines connecting the dots representing frequency of findings across studies in each group. Here, we see that studies examining within-DMN connectivity (intra-DMN) found underconnectivity involving the posterior hub of the DMN or between the anterior and posterior hubs of the DMN more frequently in ASD (Assaf et al., 2010; Weng et al., 2010; Starck et al., 2013; Doyle-Thomas et al., 2015; Jann et al., 2015; Abbott et al., 2016; Falahpour et al., 2016; Ypma et al., 2016; Duan et al., 2017; Guo et al., 2017; Pereira et al., 2018; Reiter et al., 2019; Wang et al., 2019a), while overconnectivity involving the anterior hub or between the anterior and posterior hubs of the DMN was often found in EOP studies (Tang et al., 2013; Cui et al., 2017; Wang et al., 2018a; Wang et al., 2018b; Zhang et al., 2020). Some studies reported intra-DMN underconnectivity in EOP involving the posterior hub of the DMN or between the medial and lateral hubs of the DMN (Zhang et al., 2015; Zheng et al., 2016; Wang et al., 2017a; Zhang et al., 2020). However, it should be noted that all these studies reporting intra-DMN underconnectivity in EOP are based on the same or largely overlapping subjects. On the other hand, overconnectivity within the ASD group was most frequently seen

between the anterior and lateral hubs of the DMN (Redcay et al., 2013; Abbott et al., 2016; Elton et al., 2016; Guo et al., 2017; Pereira et al., 2018). For studies examining connectivity between DMN and other brain regions (inter-DMN), underconnectivity in ASD relative to TD controls mostly involved the posterior hub of the DMN and frontal regions as well as right anterior insula, a hub region of the salience network (Wiggins et al., 2011; Doyle-Thomas et al., 2015; Nomi and Uddin, 2015; Chen et al., 2017; Bi et al., 2018; Kernbach et al., 2018; Neufeld et al., 2018; Pereira et al., 2018; Borras-Ferris et al., 2019; Guo et al., 2019). In contrast, inter-DMN underconnectivity for EOP relative to controls was seen most frequently between the anterior hub of the DMN and left temporal lobe (Zhang et al., 2015; Liu et al., 2018; Wang et al., 2018b; Zhao et al., 2018; Wang et al., 2019b). Overconnectivity for inter-DMN networks in the ASD group also involved the posterior hubs of the DMN, mostly with somatomotor and visual regions as well as anterior hubs of the DMN with the right anterior insula (Doyle-Thomas et al., 2015; Abbott et al., 2016; Elton et al., 2016; Joshi et al., 2017; Bi et al., 2018; Hogeveen et al., 2018; Pereira et al., 2018; Gao et al., 2019; Lawrence et al., 2019; Mash et al., 2019; Wang et al., 2019a). In contrast, inter-DMN overconnectivity in EOP relative to controls was predominantly observed between DMN hubs (both anterior and posterior) and the subcortex and cerebellum (Wang et al., 2016; Zhao et al., 2018; Wang et al., 2019b). Hence, it appears that intra-DMN networks seem to be more frequently underconnected (between anterior and posterior hubs) in ASD adolescents, but mixed (i.e., underconnected for anterior hub, or between medial and lateral hubs, and overconnected for posterior hub or between anterior and posterior hubs) in EOP adolescents. On the other hand, inter-DMN connectivity patterns appear to be mixed for both groups, especially in its connectivity with frontal, sensorimotor, and temporoparietal regions in ASD, and with frontal, temporal, subcortical, and cerebellar regions in EOP.

Future Directions

In this review, we have summarized resting state functional MRI studies of DMN connectivity from empirical studies in two different clinical populations involving marked social impairment, autism spectrum disorder and early onset psychosis, during the crucial developmental window of adolescence. While the literature thus far has helped shed some light on both the common and unique patterns of DMN connectivity across these two groups, several gaps remain in our understanding of how DMN connectivity might contribute to the unique

pathophysiology of both neuropsychiatric conditions. First, there have been far fewer studies on DMN connectivity in EOP than ASD adolescents. This may be due in part to difficulties in ascertaining adolescents with EOP compared to adults with psychotic disorder, given its relatively lower prevalence (Ballageer et al., 2005; Stevens et al., 2014). Another reason is the wider availability of large, open-access imaging datasets of adolescents with ASD such as ABIDE. Given the difficulties of collecting neuroimaging data in unique clinical populations at single sites, it is highly advantageous for more researchers to combine their imaging datasets using a systematic and open-source forum to allow large-scale statistical analyses cross-diagnostically. Second, both these conditions are characterized as spectrum disorders of varying severity and heterogeneous etiologies. The impact of factors such as genetic risk, symptoms endorsed, pubertal development, and treatment history on DMN connectivity have yet to be explored within both groups. For instance, few studies have examined the contribution of medication on DMN connectivity, despite evidence that antipsychotic medication can impact brain connectivity patterns (Sambataro et al., 2010; Hu et al., 2017; Wang et al., 2017b). Similarly, more work examining the impact of disease progression in EOP on DMN connectivity is needed to understand if abnormal DMN connectivity within this population remains relatively stable across the duration of illness or if further declines are associated with longer-term illness. In the ASD population, imaging studies have generally focused on high-functioning individuals, with only one study so far exploring the differences in DMN connectivity between high-and low-functioning ASD adolescents. It would be important to explore the influence of such contributing factors to DMN connectivity anomalies to interpret the divergent findings across studies and develop a potential mechanistic model of how genetics, neural wiring, and environmental factors may cascade into the phenotypic features we observe in these neuropsychiatric conditions.

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AN and CEB took the lead role in reviewing papers and drafting the manuscript. MJ and SL assisted in reviewing papers and preparing tables. All authors read and approved the final manuscript.

Conflict of Interests

The authors declare that they have no competing interests.

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Table 1. Demographic details for studies on DMN functional connectivity in adolescents with ASD

Study	Sample Size	Age		Sex (F%)	IQ
	N (ASD/TD)	ASD Mean (SD)	TD Mean (SD)	ASD/TD	
Assaf et al. 2010	30 (15/15)	15.7 (3)	17.1 (3.6)	6.7%/13.3%	ASD IQ=113.3±15.0 TD IQ=117.1±16.9
Weng et al. 2010	31 (16/15)	15(1.45)	16(1.44)	12.5%/6.7%	No Full-Scale IQ ASD VIQ=114±18.58 ASD NVIQ=117±13.82 TD VIQ=113±14.10 TD NVIQ=106±12.53
Wiggins et al. 2011	80 (39/41)	14(2.08)	15.3(2.4)	17.9%/19.5%	No Full-Scale IQ ASD VIQ=108.2±19.04 ASD NVIQ=111.54±15.97 TD VIQ=116.5±13.34 TD NVIQ=105.4±11.51
Redcay et al. 2013	28 (14/14)	17.8(1.9)	17.7(1.8)	0%/0%	ASD IQ=116.9±13.7 TD IQ=119±9.6
Starck et al. 2013	50 (24/26)	14.9(1.4)	14.8(1.7)	25%/26.9%	ASD IQ=107.3±16.9 TD IQ Not Reported
Nielsen et al. 2014	964 (447/517)	16.6(8.1)	16.9(7.56)	11.4%/17.6%	ASD IQ=105±17.4 TD IQ=112±13.3

Study	Sample Size	Age		Sex (F%)	IQ
	N (ASD/TD)	ASD Mean (SD)	TD Mean (SD)	ASD/TD	
Doyle-Thomas et al. 2015	115 (71/44)	12.3(3.1)	12.2(3.8)	0%/0%	ASD IQ=97.8±19.7 TD IQ=117.2±9.7
Jann et al., 2015	39 (22/17)	13.8(2.0)	12.8(3.6)	23.5%/13.6%	ASD IQ=107.8±18.7 TD IQ=107.8±14.3
Nomi et al. 2015	56 (28/28)	13.71(1.79)	14.01(1.74)	17.9%/17.9%	ASD IQ=103.57±15.45 TD IQ=105.18±9.90
Abbott et al. 2016	75 (37/38)	13.9(2.6)	13(2.6)	13.5%/21%	No Full-Scale IQ ASD VIQ=105±19.3 ASD NVIQ=104±16.0 TD VIQ=107.8±11.8 TD NVIQ=107.5±12.5
Elton et al. 2016	185 (90/95)	13.1(3.3)	13.2(3.1)	0%/0%	Not Reported
Falahpour et al. 2016 (Study 1)	152 (76/76)	16.1(4.9)	15.8(4.5)	11.8/15.8%	**Study 1:** ASD IQ=106.6±18.1 TD IQ=108.1±12.4
Falahpour et al. 2016 (Study 2)	64 (32/32)	14.3(2.4)	13.5(2.7)	12.5%/15.6%	**Study 2:** ASD IQ=106.3±18.0 TD IQ=109.5±11.1
Ypma et al. 2016	134 (51/40) 43 Unaffected Siblings	ASD M 14.5(1.7) ASD F 14.5(2.0) M Sib 15.0(2.1) F Sib 14.6(2.2)	M 14.8(1.7) F 15.3(5.3)	31.4%/50% Siblings 69.8%	ASD M IQ=108±16.1 M Sib IQ=113.5±11 ASD F IQ=97.6±10.7 F Sib IQ=112±9.6

Study	Sample Size	Age		Sex (F%)	IQ
	N (ASD/TD)	ASD Mean (SD)	TD Mean (SD)	ASD/TD	
					TD M IQ=114±11.4 TD F IQ=110.7±10.9
Chen et al. 2017	46 (22/24)	13.1(3.1)	15.4(1.6)	31.8%/29.2%	ASD IQ=95.2±22.1 TD M=104±18.3
Duan et al. 2017	213 (91/122)	14.87(1.61)	15(1.61)	0%/0%	ASD IQ=107.45±12.11 TD IQ=109.30±11.08
Guo et al. 2017	54 (28/26)	13.79(1.79)	14.46(1.45)	17.9%/19.2%	ASD IQ=108.06±13.86 TD IQ=110.11±7.87
Joshi et al. 2017	31 (15/16)	21.6(3.7)	21.9(3.5)	0%/0%	ASD IQ=111±10 TD IQ=123±9.2
Bi et al. 2018	92 (50/42)	13.34(2.41)	13.05(1.82)	10%/14.3%)	ASD IQ=99.73±14.40 TD IQ=107.21±10.94
Hogeveen et al., 2018	102 (49/53)	17.39(3.1)	16.8(2.95)	12.2%/23.3%	ASD IQ=103.65±14.46 TD IQ=108.81±10.76
Kernbach et al. 2018	718 (369/349)	13.53	13.54	0%/0%	Not reported
Neufeld et al. 2018	150 (62/10)	16.16(1.21)	16.16(1.21)	45.2% F	ASD IQ=100.5±16.05
Pereira et al., 2018	51 (22/29)	17.45(3.29)	18.48(2.82)	18.2%/34.5%	ASD IQ=99.77±9.5 TD IQ=105.83±9.64
Borras-Ferris et al. 2019	98 (49/49)	14.35(1.77)	14.35(1.77)	0%/0%	Not reported but groups matched for IQ (±10 points)

Study	Sample Size	Age		Sex (F%)	IQ
	N (ASD/TD)	ASD Mean (SD)	TD Mean (SD)	ASD/TD	
Guo et al. 2019	507 (209/298)	16.5(6.2)	16.8(6.2)	0%/0%	ASD IQ=110.6±13.4 TD IQ=110.2±11.4
Lawrence et al. 2019 (Time 1)	38 (16/22)	12.5(0.8)	12.9(0.9)	6.3%/0%	ASD IQ=101.3±17.7 TD IQ=107.8±13.5
Lawrence et al. 2019 (Time 2)	38 (16/22)	15.5(0.8)	16.0(0.9)	6.3%/0%	
Mash et al. 2019	119 (62/57)	13.7(2.5)	13.1(2.9)	16.1%/19.3%	ASD IQ=103±18 TD IQ=108±12
Reiter et al. 2019	88 (44/44)	11.2(2.7)	10.9(2.8)	~22%/~22%	Low ASD IQ=77±6 High ASD IQ=123 ± 8 Average TD IQ=99±7 High TD IQ=124±8
Wang et al. 2019a	260 (83/177)	11.2(5.3)	11(4)	16.9%/24.9%	No Full-Scale IQ ASD NVIQ=105.0±15.7 TD IQ=106.1±11.2
Gao et al. 2019	102 (52/50)	13.7(2.6)	13.6(2.6)	15.38%/16%	ASD IQ=104±16.4 TD IQ=107±11

Table 2. Summary of results for studies on DMN functional connectivity in adolescents with ASD

Study	Open Source Dataset	Analysis Type	Results for ASD group
Assaf et al. 2010		ICA	Underconnectivity within DMN hubs of precuneus (PCUN), and medial prefrontal cortex (mPFC).
Weng et al. 2010		Seed based analysis	Underconnectivity between posterior cingulate cortex (PCC) hub of DMN and 9 of 11 other DMN regions – retrosplenial cortex, and bilateral mPFC, superior frontal gyri (SFG), temporal lobe, parahippocampal gyri (PHG).
Wiggins et al. 2011		SOM	Underconnectivity between posterior hubs of DMN and right (r) SFG.
Redcay et al. 2013		Seed based analysis	Overconnectivity between anterior (a) MPFC hub of the DMN and right lateral parietal (rLP) seed.
Starck et al. 2013		ICA	Underconnectivity between anterior and posterior DMN subnetworks.
Nielsen et al. 2014	ABIDE	Seed based analysis	Reduced left lateralization in connectivity between PCC hub of DMN and language regions (Wernicke's area).
Doyle-Thomas et al. 2015		Seed based analysis	Mixed results with underconnectivity between left PCC hub of DMN and left (l) MPC, right inferior temporal gyrus (rITG), and bilateral angular gyri (AG). In contrast, overconnectivity between PCC

Study	Open Source Dataset	Analysis Type	Results for ASD group
			hub and inferior parietal lobule (IPL), superior parietal gyri (SPG), SFG, middle frontal gyri (MFG) and precentral gyri (PreCG).
Jann et al., 2015		ICA/Seed based analysis	Mixed results with local overconnectivity in dorsal (d) anterior cingulate cortex (ACC) but underconnectivity between dACC and PCC/PCUN hub of DMN.
Nomi et al. 2015	ABIDE	ICA	Children showed within-DMN overconnectivity but not adolescents; Adolescents showed underconnectivity between DMN and subcortical/insular network.
Abbott et al. 2016		Seed based analysis	Mixed results with underconnectivity within mPFC and PCC hubs of the DMN and overconnectivity between PCC and right ventrolateral prefrontal cortex (rVLPFC) and rIPL, mPFC and rVLPFC, and lAG and right dorsolateral prefrontal cortex (rDLPFC) and rIPL.
Elton et al. 2016	ABIDE	Seed based analysis	Overconnectivity between bilateral mPFC hub of DMN with bilateral IPL and right anterior insula (AI).
Falahpour et al. 2016	ABIDE	DFC/Seed based analysis	Greater temporal variability across windows, as well as predominant underconnectivity within DMN regions such as PCC with mPFC, ACC, and right hippocampus, and mPFC with lLP.

Study	Open Source Dataset	Analysis Type	Results for ASD group
Ypma et al. 2016	ABIDE	Seed based analysis	Underconnectivity within-DMN network in both males and females with ASD even compared to unaffected siblings.
Chen et al. 2017	ABIDE	SVM	Atypical connectivity within DMN and salience network in both ASD and EOP. Distinct atypical connectivity for ASD was within-salience network.
Duan et al. 2017	ABIDE	DFC/Seed based analysis	Underconnectivity within-DMN regions, between DMN and visual as well as ventral attention network in lower frequency bands (slow-4, slow-5).
Guo et al. 2017	ABIDE	ALFF	Mixed results with lower ALFF values in rPCUN hub of DMN, and higher ALFF values in mPFC hub of DMN only for adolescents.
Joshi et al. 2017		Seed based analysis	Mixed results with underconnectivity between mPFC hub of DMN and bilateral AG region, and overconnectivity between DMN coupling with task positive fusiform face are (FFA) and supramarginal gyri (SMG).
Bi et al. 2018	ABIDE	ICA	Mixed results with underconnectivity within anterior hubs of the DMN of mPFC, inferior frontal gyrus-triangularis (IFGtriang) and overconnectivity with posterior hubs of the DMN (PreCG, SPG, PCUN).

Study	Open Source Dataset	Analysis Type	Results for ASD group
Hogeveen et al., 2018		Seed based analysis	Overconnectivity between DMN and salience as well as frontoparietal network.
Kernbach et al. 2018	ABIDE	SVM	Underconnectivity between DMN and salience network and lower coupling of DMN and right temporoparietal junction (rTPJ) node of dorsal attention network.
Neufeld et al. 2018		Seed based analysis	Underconnectivity between DMN (PCC, vmPFC) and salience network (ACC, rAI) hubs in adolescents.
Pereira et al., 2018		Seed based analysis	Mixed results with underconnectivity between PCC hub and executive control component of DMN (ACC, IFG, SFG, middle temporal regions), and overconnectivity between mPFC hub and sensorimotor component of DMN (amPFC, bilateral Pre-and Post-CG).
Borras-Ferris et al. 2019	ABIDE	Seed based analysis	Underconnectivity between rPCUN hub of DMN and right middle temporal gyrus (rMTG) as well as bilateral Post-CG.
Guo et al. 2019	ABIDE	DFC/Seed based analysis	Underconnectivity within vmPFC and PCC hubs of the DMN with rAI in social cognition dynamic states (state 3, state 5).
Lawrence et al. 2019	ABIDE II	Seed based analysis	Atypical developmental trajectory with lower negative connectivity between DMN and central

Study	Open Source Dataset	Analysis Type	Results for ASD group
			executive network longitudinally from early to late adolescence.
Mash et al. 2019		Static connectivity and DFC/ICA	Overconnectivity between DMN and visual, sensorimotor, frontoparietal, and executive network in static state; along with increased variability in DMN across dynamic states.
Reiter et al. 2019	ABIDE II	Seed based analysis	Underconnectivity within-DMN in lower-functioning participants more prominent than higher-functioning participants.
Wang et al. 2019a	ABIDE II	ICA	Mixed results with underconnectivity within-DMN regions, and overconnectivity between DMN and somatomotor network.
Gao et al. 2019		Seed based analysis	Overconnectivity between PCC hub of DMN and IFG and visual cortex bilaterally

Table 3. Demographic details for studies on DMN functional connectivity in adolescents with EOP

Study	Sample Size	Age		Sex (F%)	Education in Years
	N (EOP/TD)	EOP Mean (SD)	TD Mean (SD)	EOP/TD	
Tang et al. 2013	64 (32/32)	16.2(1.2)	16.4(0.9)	53.1%/50%	EOP=9.4±1.5 TD=9.7±0.7
Zhang et al. 2015	67 (37/30)	15.5(1.8)	15.3(1.6)	54.1%/43.3%	EOP=8.5±1.48 TD=8.7±1.42 IQ>70 both groups
Wang et al. 2016	102 (31/37) UHR 34	20.61(4.42) UHR 21.50(3.53)	20.76(3.08)	38.7%/51.4% UHR 38.2%	EOP=6.26±4.27 UHR =6.26±4.13 TD=5.46±1.87
Zheng et al. 2016	65 (35/30)	15.5(1.8)	15.3(1.6)	42.9%/56.7%	EOP=8.5±1.48 TD=8.7±1.42
Chen et al. 2017	66 (35/31)	15.6(1.8)	15.4(1.6)	42.86%/58.06 %	Not Reported
Cui et al. 2017	51 (32/19)	AVH 21.24(3.85) Non-AVH 22.53(4.07)	23.79(3.75)	AVH 41.18% Non-AVH 46.67% TD 47.37%	AVH=13.71±1.93 Non-AVH= 13.40±1.55 TD=14.74±2.26
Wang et al. 2017a	65 (35/30)	15.5(1.8)	15.3(1.6)	42.9%/56.7%	EOP=8.5±1.48 TD=8.7±1.42
Liu et al. 2018	79 (48/31)	15.79(1.64)	15.42(1.52)	56.3%/54.8%	EOP=8.88±1.95 TD=8.44±1.56

Study	Sample Size	Age		Sex (F%)	Education in Years
	N (EOP/TD)	EOP Mean (SD)	TD Mean (SD)	EOP/TD	
					IQ>70 both groups
Wang et al. 2018a	79 (48/31)	15.79(1.64)	15.42(1.52)	56.3/54.8%	EOP=8.88±1.95 TD=8.44±1.56 IQ>70 both groups
Wang et al. 2018b	79 (48/31)	15.79(1.64)	15.42(1.52)	56.3/54.8%	EOP=8.88±1.95 TD=8.44±1.56
Zhao et al. 2018	86 (48/38)	AVH 24.32(8.46) Non-AVH 24.35(6.94)	25.44(7.52)	AVH 53.5% Non-AVH 50% TD 55.3%	AVH=11.29±3.00 Non-AVH= 11.70±2.60 TD=13.34±3.58
Wang et al. 2019b	65 (35/30)	15.5(1.8)	15.3(1.6)	42.9/56.7%	EOP=8.5±1.48 TD=8.7±1.42
Ilzarbe et al. 2019	68 (27/41)	18.1(1.6)	17.8(1.6)	59.3%/56.1%	EOP=92.8±15.7* TD=104.1±9.8*
Zhang et al. 2020	79 (48/31)	15.79(1.64)	15.42(1.52)	56.3%/54.8%	EOP=8.88±1.95 TD=8.44±1.56 IQ>70 both groups

* Study reported IQ scores instead of education in years for demographic characteristics

Table 4. Summary of results for studies on DMN functional connectivity in adolescents with EOP

Study	Patient Characteristics	Analysis Type	Results for EOP group
Tang et al. 2013	Youth with first-episode schizophrenia <2 years illness onset	ICA/ALFF	Overconnectivity between mPFC and other areas of the DMN.
Zhang et al. 2015	Drug-naïve patients with first-episode schizophrenia <2 years illness onset	Seed based analysis	Underconnectivity between rMTG seed region of DMN and lITG, lFFA, lPHG, as well as between DMN and visual network regions.
Wang et al. 2016	Drug-naïve patients with first-episode schizophrenia < 2 years illness onset UHR included brief intermittent psychotic syndrome, attenuated positive symptom syndrome, and genetic risk and deterioration syndrome	Seed based analysis	Overconnectivity between DMN (PCUN/PCC, mPFC) and cerebellum in both EOP and UHR groups; with UHR group showing stronger patterns of cerebellar-DMN connectivity than EOP group.
Zheng et al. 2016	Drug-naïve patients with first-episode schizophrenia <2 years illness onset	Seed based analysis/ALFF	Lower ALFF values in vPCUN, along with underconnectivity between vPCUN and dPCUN as well as midcingulate cortex (MCC).
Chen et al. 2017	Drug-naïve patients with first-episode schizophrenia	SVM	Atypical connectivity within DMN and salience network in both EOP and ASD. Distinct atypical

Study	Patient Characteristics	Analysis Type	Results for EOP group
	< 2 years illness onset		connectivity for EOP was between DMN-salience connectivity.
Cui et al. 2017	Patients with schizophrenia experiencing AVHs vs. Patients with schizophrenia not experiencing AVHs	ICA/ALFF	Higher signal amplitude within-DMN regions (mPFC, ACC, PCC, AG, rSPG) along with increased prefrontal cortex-DMN coactivation in patients with AVHs versus non-AVH patients. AVH patients also demonstrated more atypical ALFF values in PCUN than non-AVH patients.
Wang et al. 2017a	Drug-naïve patients with first-episode schizophrenia <2 years illness onset	DFC	Underconnectivity in PCUN hub of DMN in slow-4 frequency band, but no significant group differences in slow-5 frequency band.
Liu et al. 2018	Drug-naïve patients with first-episode schizophrenia <2 years illness onset	SVM /ReHo	Decreased ReHo values in rPre-CG, lPost-CG, rIPL, rMFG, bilateral PCUN, left superior temporal gyrus (lSTG), left paracentral lobule regions of the DMN. Reho values in bilateral PCUN and rIPL especially discriminated patients with 91.67% sensitivity, 87.1% specificity, and 89.87% accuracy.
Wang et al. 2018a	Drug-naïve patients with first-episode schizophrenia <2 years illness onset	SVM	Mixed results with underconnectivity of both long- and short-range networks involving posterior DMN hubs, and overconnectivity of both long- and short -range networks involving anterior DMN hubs.
Wang et al. 2018b	Drug-naïve patients with first-episode schizophrenia	SVM/ReHo	Mixed results with increased ReHo values in mPFC hub of DMN, and decreased ReHo values in lSTG,

Study	Patient Characteristics	Analysis Type	Results for EOP group
	<2 years illness onset		rPre-CG, rIPL, and left paracentral lobule; this combination was able to discriminate patients from controls with the sensitivity of 88.24%, specificity of 91.89%, and accuracy of 90.14%.
Zhao et al. 2018	Drug-naïve patients with first-episode schizophrenia experiencing AVHs vs. Drug-naïve patients with first-episode schizophrenia not experiencing AVHs <2 years illness onset for both groups	GCA	Mixed results with underconnectivity between DMN hubs (mPFC, PCC) and left inferior temporal gyrus (lITG), lSTG, bilateral cingulate gyrus, bilateral thalamus, left insula, and left cerebellum, with overconnectivity between hub regions and left cingulate gyrus, right putamen, rMFG, right thalamus, and left cerebellum. AVH patients demonstrated underconnectivity between aMPFC and lITG, as well as PCC to left cerebellum, lITG, and rMFG compared to non-AVH patients.
Wang et al. 2019b	Drug-naïve patients with first-episode schizophrenia <2 years illness onset	DFC	Mixed results with underconnectivity between lPCUN hub of DMN and lMTG in state2, and overconnectivity in rPCUN, rSMG, and right putamen in state 4.
Ilzarbe et al. 2019	Youth with early onset psychosis including schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, bipolar spectrum	ICA	Underconnectivity of mPFC hub of DMN in EOP group compared to TD controls, and connectivity additionally decreased with age in EOP where it increased with age in TD controls.

Study	Patient Characteristics	Analysis Type	Results for EOP group
	disorders, and psychosis not otherwise specified <2 years illness onset		
Zhang et al. 2020	Drug-naïve patients with first-episode schizophrenia <2 years illness onset	SVM/NH	Mixed results with higher NH values in left mPFC and lower NH values in bilateral PCC/PCUN in EOP group compared to TD controls.

FIGURE CAPTION

Figure 1: A] DMN hub regions included in analyses across most studies in the present review denoted in yellow circles ; **B]** Intra-DMN connectivity findings across ASD adolescent studies (left panel) – Underconnectivity findings (denoted by red dots) mostly involve the posterior hubs of the DMN including posterior cingulate cortex (PCC) and precuneus (PCUN). Thicker lines such as between the PCC/PCUN and the anterior hubs of the DMN including the medial prefrontal regions (mPFC) and anterior cingulate cortex (ACC) denote overlapping findings across multiple studies (Refs), with thinner lines indicating underconnectivity within DMN regions found in fewer studies. Overconnectivity findings (denoted by blue dots) for the ASD group involve the anterior hubs of the DMN slightly more prominently than the posterior hubs on the DMN. Thicker lines such as between the mPFC and left and right inferior parietal lobule (lIPL, rIPL) denote overlapping findings across multiple studies, with thinner lines indicating overconnectivity within DMN regions found in fewer studies. Intra-DMN connectivity findings for EOP adolescent group are depicted in the right panel – Underconnectivity within the DMN regions (red dots) was found by fewer studies for this group indicated by thinner lines, while overconnectivity (blue dots) was mostly found within the anterior and posterior hubs of the DMN; **C]** Inter-DMN connectivity findings across ASD adolescent studies (left panel) – Underconnectivity findings (denoted by red dots) mostly involve the posterior hub (PCC/PCUN) of the DMN especially in its connectivity with prefrontal regions and the right anterior insula (rAI) hub of the salience network denoted by thicker lines with additional findings of underconnectivity between DMN and other brain regions denoted by thinner lines. Overconnectivity findings (denoted by blue dots) for the ASD group also involve the posterior hubs of the DMN mostly with somatomotor regions as well as anterior hubs of the DMN with the salience network hub (rAI) denoted by thicker lines. Other regions demonstrating overconnectivity with the DMN for the ASD group are denoted by thinner lines. Inter-DMN connectivity findings for EOP adolescent group are depicted in the left panel – Underconnectivity between anterior DMN hubs and left temporal lobe was most prominently found across studies depicted by thicker lines, with additional findings of underconnectivity between both the anterior and posterior hubs of the DMN and other brain regions denoted by thinner lines. On the other hand,

overconnectivity in the EOP group was predominant between DMN hubs (both anterior and posterior) and the subcortex and cerebellum highlighted by thicker lines, with additional overconnectivity between DMN hubs and other brain regions denoted by thinner lines. Additional abbreviations used in figure: PHG - parahippocampal gyrus, AG – angular gyrus, LatP – lateral parietal lobule, SFG – superior frontal gyrus, IFG – inferior frontal gyrus, PreCG – precentral gyrus, POSTCG – postcentral gyrus, ITG – inferior temporal gyrus, TPJ – temporoparietal junction, MFG – middle frontal gyrus, DLPFC – dorsolateral prefrontal gyrus, FFA – fusiform face area, SPG – superior parietal gyrus, SMG – supramarginal gyrus, CING – cingulate gyrus, Thal – thalamus, MTG – middle temporal gyrus, STG – superior temporal gyrus, PUT – putamen.