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Putative Brain Networks Underlying Repetitive Negative Thinking and Comorbid Internalizing Problems in Autism

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Abstract

Many high-functioning individuals with autism spectrum disorder (ASD) also experience depression and anxiety, yet little is known about mechanisms underlying this comorbidity. Repetitive negative thinking (RNT) about self-referential information is a transdiagnostic cognitive vulnerability factor that may account for the relationship between these two classes of symptoms. We propose a model where self-referential processing and cognitive inflexibility interact to increase risk for RNT, leading to internalizing problems in ASD. Examination of interactions within and between two well-characterized large-scale brain networks, the default mode network and the salience network, may provide insights into neurobiological mechanisms underlying RNT in ASD. We summarize previous literature supporting this model, emphasizing moving towards understanding RNT as a factor accounting for the high rates of internalizing problems in ASD. Future research avenues include understanding heterogeneity in clinical presentation, and promise for identifying and treating cognitive flexibility and RNT to reduce comorbid internalizing problems in ASD.

Keywords

Autism spectrum disorder; anxiety; depression; rumination; worry; salience network; default mode network

The high rates of comorbidity among mental health disorders has led to a search for endophenotypes with a genetic or neurological basis that contribute to maladaptive functioning across clinical conditions (Insel, 2014). Repetitive negative thinking (RNT) refers to the process of perseverating on negative information about one's self, or emotional problems and experiences (Ehring et al., 2011; McEvoy, Mahoney, & Moulds, 2010). These repetitive self-focused thoughts are intrusive, difficult to disengage from, and cause impairment to the individual. RNT is a product of both negative self-referential cognitions and inflexible thinking. Though the *content* of the repetitive thoughts varies across individuals, the *process* and hypothesized underlying neural *mechanism* is thought to be consistent across individuals who engage in RNT (Ehring & Watkins, 2008; Ehring et al., 2011; Nolen-Hoeksema, Wisco, & Lyubomirsky, 2008). Perseverative cognitive processes,

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specifically RNT, are present across many forms of psychopathology, and likely contribute to maladaptive functioning (Arditte, Shaw, & Timpano, 2016).

Research on RNT has almost exclusively examined sub-facets of the more general phenomena, which include rumination, worry, and post-event processing (McEvoy et al., 2010). These processes were hypothesized to differ in the content and temporal orientation (past, present, future) of the thoughts, and were historically considered to reflect disorder-specific symptoms. As such, most studies examining these cognitive processes compare one specific clinical group (e.g., depression, anxiety) to healthy controls. Studies of the neural basis for RNT have focused almost exclusively on the default mode network, which is thought to support self-focused thought (Gusnard, Akbudak, Shulman, & Raichle, 2001; Raichle et al., 2001). However, emerging evidence suggests that RNT is an encompassing phenomenon that increases risk for internalizing problems across clinical groups, with a biological basis involving multiple large-scale brain networks. Here, we discuss the implications of studying the broader RNT phenomenon in autism, a disorder with frequent comorbid internalizing problems, and explore the possibility that brain networks involved in flexible switching of attention, such as the salience network (Seeley et al., 2007; Uddin, 2015), may also contribute to RNT. Expanding the research on RNT to varied clinical groups and probing the involvement of multiple, interacting large-scale neural systems will lead to a better understanding of the construct and its relationship to internalizing problems.

Autism Spectrum Disorder and Comorbid Anxiety and Depression

Autism spectrum disorder (ASD) affects an estimated 1 in 68 children (CDC, 2014), and reflects a neurodevelopmental disorder characterized by socio-communication deficits and repetitive thoughts and behaviors (APA, 2013; Wingate et al., 2014). Anxiety and depression disorders and sub-clinical symptoms are rife across the lifespan in individuals on the autism spectrum, and impair functioning over time (Mayes, Calhoun, Murray, & Zahid, 2011; Simonoff et al., 2008; White, Oswald, Ollendick, & Scahill, 2009). Parents of most children with ASD endorse some symptoms of anxiety and depression in their child, particularly in higher-functioning children with autism (Mayes et al., 2011). Additionally, approximately 40% of children with ASD meet criteria for an anxiety disorder, and 2–38% of children meet criteria for depression, with similar estimates in adult samples (Lainhart, 1999; Simonoff et al., 2008).

There is considerable variability in the presence, expression, and impairment caused by symptoms of autism, as well as symptoms of depression and anxiety in ASD (Kerns et al., 2014; Wing & Gould, 1979). Differentiating these symptoms as resulting from either ASD or an affective disorder has proven difficult due to shared behavioral manifestation of symptoms of ASD with internalizing problems (e.g., social withdrawal, reduced eye contact, emotional dysregulation). In addition, symptoms of ASD and associated social impairments may also interact with symptoms of anxiety and depression over time and across development. For example, difficulties in social situations may reinforce patterns of avoidance, which in turn make future social endeavors more difficult (Bellini, 2004). However, due to an early misconception by researchers that individuals with ASD do not possess the insight or cognitive capacity to reflect on their social interactions, little research

has examined the processes or mechanisms that contribute to the comorbidity between ASD and affective symptoms (Gotham, Bishop, Brunwasser, & Lord, 2014; Kerns et al., 2014; Mundy, Henderson, Inge, & Coman, 2007). These limitations highlight the imperative need to understand cognitive and neural vulnerability factors that contribute to the high rates of anxiety and depression in ASD in order to design treatments to ameliorate these symptoms.

RNT may be one key mechanism linking autism symptoms and related impairments with co-occurring internalizing problems (Gotham et al., 2014; Mazefsky, Pelphrey, & Dahl, 2012). Impaired disengagement from distressing self-referential material has been proposed as a crucial risk factor for RNT (Gotlib & Joormann, 2010; Koster, De Lissnyder, Derakshan, & De Raedt, 2011). Thus, difficulties with flexible switching of attention in response to distressing events, as well as heightened self-focused attention could independently and jointly predict increased RNT. To date, this model has remained relatively unexplored in populations characterized by impaired cognitive control (Snyder, Miyake, & Hankin, 2015), particularly ASD.

Symptoms of ASD, in addition to common associated traits of autism, may heighten the risk for RNT. This in turn could explain the high prevalence of internalizing problems in ASD. Individuals with ASD exhibit core symptoms of difficulties with social communication and restricted and repetitive behaviors that are observable by age two (APA, 2013). In addition, deficits in cognitive flexibility, or the ability to adaptively switch between mental processes to produce appropriate behavioral responses (Scott, 1962), are often noted in both children and adults with ASD (Dajani & Uddin, 2015; Lopez, Lincoln, Ozonoff, & Lai, 2005; Panerai et al., 2014). Furthermore, individuals with ASD appear to be temperamentally predisposed to negative affect, which may heighten the salience of negative information (Burrows, Usher, Schwartz, Mundy, & Henderson, 2016; Garon et al., 2009). Here, we adapt and extend the impaired disengagement model (Koster et al., 2011) to ASD (Figure 1). We propose that the inflexible cognitive style that characterizes ASD, in conjunction with insight into one's social difficulties, may contribute to RNT in the disorder and subsequently increase risk for co-occurring internalizing problems. We also discuss putative neural mechanisms underlying these processes, involving interactions within and between the default mode network and salience network. In contrast to the initial model described by Koster and colleagues (Koster et al., 2011), which contended that cognitive control of emotion (subserved by the central executive network) plays a role in disengaging from distressing self-referential thoughts, we posit that inflexible attention allocation (subserved by the salience network) may predispose individuals to RNT. While individual aspects of our theory have been supported in the disorder-specific clinical (e.g., depression, anxiety, ASD) literature, no theoretical model to date has comprehensively explicated the inter-relations among these factors in ASD. Furthermore, the artificial distinction of rumination and worry in previous work on individuals with ASD has hindered our understanding of shared and divergent risk for co-occurring depression and anxiety in ASD.

There are several unique considerations when examining RNT in general, and in ASD. Considerable heterogeneity is present across domains in the population of individuals with ASD (APA, 2013; Jeste & Geschwind, 2014; Wing, 1997). The model we propose here applies to verbally-fluent individuals who are capable of reporting on their own cognitive

styles. Our review focuses on higher-functioning individuals with ASD who are able to self-report on their cognitions. These types of self-reports typically become reliable around age 9 (Bijttebier, Raes, Vasey, Bastin, & Ehring, 2015). It is also at this developmental stage (e.g., middle childhood), when an individual's sense of self becomes highly influenced by feedback from social encounters, and when cognitive flexibility reaches mature levels (Anderson, 2002). Thus, middle childhood is likely the first developmental period during which RNT can be reliably assessed.

Heterogeneity of the content of thoughts may also present unique considerations to the model we propose. Due to the heterogeneity of interests of individuals with ASD, the content of negative thoughts may differ within and across individuals with the disorder (Lam & Aman, 2007; Mazefsky et al., 2012). Not all repetitive thoughts in ASD may cause impairment to internal functioning (e.g., a child repetitively thinking about train schedules). Thus, similar to work in the mood and anxiety disorder literature (e.g., McEvoy et al., 2010), differentiating negative self-referential perseverative thoughts from other types of repetitive thoughts will be important in determining contributions to maladaptive functioning in ASD (Marchetti, Van de Putte, & Koster, 2014; Nejad, Fossati, & Lemogne, 2013).

Studying RNT as a unitary construct in ASD has several promising implications. First, as there are no studies examining RNT, or its component processes in relation to both depression and anxiety in ASD, it is at present impossible to determine potential common or differential risk for developing anxiety or depression. To determine whether the construct of RNT confers similar risk for depression and anxiety, it is imperative to study the process of RNT in ASD in association with both of these symptoms. Second, individuals with autism are often quite literal in their interpretation of questionnaires (Ehlers, Gillberg, & Wing, 1999), a limitation of previous research that the domain-general nature of RNT effectively circumvents. Using a measure that includes content specific to one disorder might underestimate levels of RNT in an individual with ASD. Focusing on the *process* of perseverating on self-referential information will help capture the full variability in the RNT construct. Third, very little is known about the underlying neural processes that contribute to RNT in ASD. Identifying the neural basis for RNT may help identify individuals at highest risk for co-occurring psychopathology, as well as uncover potential associations with core ASD symptoms. This may help identify novel treatments for these co-occurring problems. If RNT is related to cognitive inflexibility in ASD, treatments that promote flexible thinking in stressful situations may offset risk, or reduce symptoms of depression and anxiety, improving the quality of life for individuals with autism and their families.

Here we review the previous research on the construct RNT, particularly as it applies to ASD. We focus specifically on the components of rumination and worry, as there are no studies to our knowledge of post-event processing, or the broader process of RNT in ASD. We then describe findings from the clinical and developmental literatures on measures and neural mechanisms underlying RNT. In reviewing previous research, we will use the terms the authors originally used in describing the sub-facets of RNT (e.g., rumination, worry). However, we will use the more encompassing term RNT, when discussing future directions for research in ASD populations, describing necessary advances and implications for treatment.

Defining and Measuring Components of RNT

The two subfacets of RNT that are most relevant to ASD are rumination and worry. Rumination involves passively focusing on distressing thoughts in response to sad mood and negative experiences (Nolen-Hoeksema, 1991, 2004). Rumination is most frequently measured using the Ruminative Responses Scale (Nolen-Hoeksema & Morrow, 1991; Treynor, Gonzalez, & Nolen-Hoeksema, 2003), which assesses self-focused and symptom-focused thoughts, as well as the consequences of these negative thoughts in response to negative events. Worry refers to a tendency to dwell on difficulties, and perceive future problems as more likely than they are in reality, and is typically assessed using the Penn State Worry Questionnaire (Meyer, Miller, Metzger, & Borkovec, 1990). Though descriptions of rumination and worry sound very similar, they developed in the distinct fields of depression and anxiety research. Thus, the measures of rumination and worry both include disorder-specific content. For example, the Penn State Worry Questionnaire (Meyer et al., 1990) includes the term “worry,” a core symptom of Generalized Anxiety Disorder, in every question. Thus, the narrow use of vocabulary in this questionnaire may overestimate the specific association between worry and anxiety, masking some of the overlap between worry and rumination, as well as joint contributions to symptoms of both anxiety and depression (McEvoy et al., 2010).

Although rumination and worry were initially identified through independent fields of research, recent reports have identified similarities in these cognitive processes, suggesting they may reflect the same transdiagnostic construct (McEvoy et al., 2010; Treynor et al., 2003; Watkins, 2008). These findings have supported the need for measures that are independent from symptoms of depression and anxiety. McEvoy and colleagues (2010) adapted items from the Ruminative Responses Scale, the Penn State Worry Questionnaire, and the Post-Event Processing Questionnaire (McEvoy & Kingsep, 2006) to remove disorder-specific content, and found that items assessing RNT loaded together in a factor analysis. Thus, researchers developed the Repetitive Thinking Questionnaire (RTQ), which assesses the process of RNT. A similar measure has been developed by other groups, including the Perseverative Thinking Questionnaire (PTQ; Ehring et al., 2011), which also has a version that has been validated in children as young as 9 years of age (Bijttebier et al., 2015). These questionnaires assess the core aspects of RNT, including the presence of repetitive, intrusive thoughts that are difficult to disengage from, are perceived as unproductive, and capture mental capacity. Importantly, these generalized RNT measures appear to relate comparably to levels of anxiety and depression in children (Bijttebier et al., 2015) and adults (Arditte et al., 2016; Ehring et al., 2011; McEvoy, Watson, Watkins, & Nathan, 2013).

Neural Correlates of RNT

Complex cognitive processes arise from the coordination of multiple brain regions (Mesulam, 1990). Current conceptualizations of brain function contend that local and distal brain regions are functionally coupled, and operate within networks to achieve specific outcomes (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995; Damoiseaux et al., 2006; Pessoa, 2014; Smith et al., 2009). Three canonical large-scale brain networks have been

identified due to their ubiquitous involvement across multiple task domains. The executive control network is involved in externally directed, attention-demanding tasks with primary nodes in the posterior parietal cortex and dorsolateral prefrontal cortex (Fox et al., 2005; Miller & Cohen, 2001; Seeley et al., 2007). Internally directed self-referential thinking is subserved by the default mode network (Spreng, Mar, & Kim, 2008), comprised of cortical midline structures including the medial prefrontal cortex, subgenual anterior cingulate cortex and posterior cingulate cortex. Finally, the salience network, comprised of the dorsal anterior insula, the dorsal anterior cingulate cortex, and subcortical structures, including the amygdala (Seeley et al., 2007), is involved in attention allocation and initiating dynamic switches between other large-scale brain networks (Sridharan, Levitin, & Menon, 2008; Uddin, 2015). Dynamic interactions between these networks, and efficient switching between internally- and externally-directed thought by the salience network is hypothesized to contribute to coordination between cognition and emotion, with aberrant coordination leading to various forms of psychopathology (Menon, 2011; Uddin, 2015), including ASD (Uddin & Menon, 2009).

RNT is likely a product of both negative self-referential cognitions and inflexible thinking. Currently, most studies of the neural basis for RNT have focused on connectivity within the default mode network due to its involvement in self-focused thought (Kelley et al., 2002; Murray, Schaer, & Debbané, 2012). Although no studies have yet examined the neural underpinnings of RNT using a content-independent measure, a growing body of neuroimaging research investigates the neural correlates of similar cognitive processes (e.g., rumination and worry). Depression is characterized by hyper-connectivity of the default mode network, and difficulty disengaging these structures during cognitively-demanding tasks (Kerestes, Davey, Stephanou, Whittle, & Harrison, 2014; Mayberg et al., 2005). Aberrant connectivity between regions of the default mode network, specifically the posterior and anterior nodes, has been repeatedly implicated in rumination and depression across development (Berman et al., 2010; Connolly et al., 2013). Intrinsic functional connectivity between default mode network nodes has been related to levels of rumination in both depressed and healthy individuals (Berman et al., 2010). Another study by the same group showed that, during periods of induced rumination, depressed individuals showed increased connectivity relative to baseline in the default mode network (Berman et al., 2014). Thus, increased connectivity within the default mode network is a hallmark of depression, and is also exacerbated during induced RNT.

A possibility that has received less attention in the neuroimaging literature is that RNT arises from maladaptive switching of attention that reflects cognitive inflexibility. If this is the case, connectivity within and between other networks in addition to the default mode network may contribute to RNT. Cognitive flexibility requires deployment of executive functions, such as inhibition of responses, sustained attention, and working memory (Dajani & Uddin, 2015; Snyder et al., 2015). These executive functions arise from coordination of fronto-parietal brain regions, including regions of both the salience and executive control networks. Recent research increasingly suggests that the salience network is involved in cognitive flexibility due to its role in attention orienting and switching between mental states (Uddin, 2015). Thus, we hypothesize that salience network dysfunction may also contribute to RNT processes.

In support of this hypothesis, activation in, and connectivity between the salience and default mode networks also relates to levels of rumination and depression. Specifically, intrinsic functional connectivity between the insular cortex (a node of the salience network) and subgenual anterior cingulate cortex (a node of the default mode network) along with task-induced increases in functional connectivity while ruminating have been related to depression in both adolescents and adults (Berman et al., 2014; Connolly et al., 2013). Activity in both the insula and the subgenual anterior cingulate cortex are modulated by inducing sadness (Mayberg et al., 1999) and autobiographical recall of sad memories in typical adults (Harrison et al., 2008). Finally, emerging evidence suggests that altered insula timing and coordination between large-scale networks may underlie RNT. Specifically, the timing of insula activity in relation to network switching between the default mode and executive control networks appears to differ in depressed individuals (Hamilton et al., 2011). Variability in connectivity between the insula and nodes of the default mode network also differs in depressed individuals, and is related to rumination scores (Kaiser et al., 2016). One of the main functions of the anterior insula is detecting salient information (Uddin, 2015). Atypical timing and coordination of the insula with brain regions involved in self-referential processing may be indexing heightened salience of negative self-referential material to individuals with depression. While less studied in RNT, the degree and timing of activation of brain regions that comprise the salience network, as well as connectivity between the salience and default mode networks appear to serve important functions in the onset and maintenance of RNT.

Similar results emerge in the few studies investigating the neural correlates of worry and rumination. Paulesu and colleagues induced worry in adult patients with generalized anxiety disorder (GAD) and healthy controls (Paulesu et al., 2010). Inducing worry increased activity in the medial prefrontal cortex, a core region of the default mode network, and the dorsal anterior cingulate cortex in the salience network. They found that this induction had more enduring effects on the GAD patients, where signal differences persisted beyond the mood induction. Specifically, signal differences in the dorsal anterior cingulate cortex differentiated high and low worriers, and related to scores on the Penn State Worry Questionnaire. Another study of university-aged women with varying levels of worry found similar results (Servaas, Riese, Ormel, & Aleman, 2014). In this study, activation of cortical midline structures of the default mode network, as well as the anterior insula was modulated by induced worry. These findings support the joint roles of the default mode and salience networks in increasing risk for RNT.

RNT in ASD: Rumination and Worry

Several recent studies (Table 1) have examined rates and correlates of rumination in individuals with high-functioning autism (verbal IQ > 70). There are no studies of rumination in lower-functioning, or non-verbal individuals with ASD, largely due to the verbal and cognitive demands of completing self-reported questionnaires assessing thinking styles. All studies have found strong, positive associations between rumination and depression symptoms, both concurrently (Crane, Goddard, & Pring, 2013; Gotham et al., 2014; Mazefsky, Borue, Day, & Minshew, 2014; Rieffe et al., 2011) and predictively (Rieffe, De Bruine, De Rooij, & Stockmann, 2014). In a longitudinal study, rumination level was a

better predictor of developing depression than other emotion regulation strategies examined both in children with ASD and typically developing children (Rieffe et al., 2014). Rumination has been shown to independently predict depression symptoms, but may also interact with other characteristics that may exacerbate depressive symptoms. In one recent study of high-functioning adolescents and adults with ASD, rumination interacted with perceived impairment from symptoms of ASD, such that those with negative self-evaluations, who also perseverated on previous experiences exhibited the highest rates of depression (Gotham et al., 2014). Findings from this study support the joint contributions of insight into social difficulties and cognitive inflexibility to depressive symptoms.

Adolescents (Crane et al., 2013; Mazefsky et al., 2014) and adults (Gotham et al., 2014) with ASD consistently endorse higher levels of rumination than neurotypical individuals, with mean levels closer to those of depressed samples. However, children with ASD exhibit comparable levels of rumination to typically developing children (Rieffe et al., 2014; Rieffe et al., 2011). While measurement issues may contribute to this discrepancy, it is also plausible that there is a developmental trend for increased rumination in ASD beginning in adolescence. The great heterogeneity in negative self-referential processes in ASD may also mask group differences relative to neurotypical populations. It may also be that certain individuals with ASD exhibit heightened RNT as early as middle childhood, which could lead to heightened internalizing problems in adolescence, when peer interactions become more salient, but also less predictable (Brown, 2004; Picci & Scherf, 2014). However, other individuals with ASD may exhibit lower than average levels of RNT due to limited insight or ability to report on their cognitive processes, which may be especially pronounced at younger ages. Thus, the variability in RNT due to heterogeneity within ASD may mask group differences at early ages. Additionally, no studies of rumination in ASD have assessed symptoms of anxiety, so the similarity or specificity of associations with depression and anxiety symptoms has not been tested.

To date, only a handful of studies have examined worry in children with ASD, and no study to our knowledge has examined worry in a sample of adults with autism. Early in development, children with ASD endorse higher levels of worry than TD children. For example, approximately 45% of children with ASD as young as 8 years of age endorsed an item assessing worry, in contrast to only 10% of typically developing children (Worley & Matson, 2011). Similarly, several studies have found elevated social worries on both parent- and self-reports (Gillott, Furniss, & Walter, 2001; Russell & Sofronoff, 2005). One study conducted exploratory factor analysis on common comorbid conditions in ASD. Interestingly, the factor that most closely matches RNT, with items assessing recurring thoughts and worry, showed strong, comparable associations with both depression and anxiety, further supporting the notion of RNT as a shared risk factor for internalizing problems in ASD (Matson, LoVullo, Rivet, & Boisjoli, 2009).

Characteristics of ASD may also put individuals with the disorder at increased risk for RNT and internalizing problems. Specifically, cognitive inflexibility, and insistence on sameness have also been associated with elevated internalizing problems in ASD (Hollocks et al., 2014; Lawson et al., 2015; Rodgers, Glod, Connolly, & McConachie, 2012). Additionally, behavioral measures of cognitive flexibility have been associated with aspects of RNT (e.g.,

rumination) in depressed individuals (De Lissnyder et al., 2012; Demeyer, De Lissnyder, Koster, & De Raedt, 2012; Snyder, 2013). However, there is currently a lack of research examining the relationship between cognitive inflexibility, the process of RNT, and internalizing problems in ASD.

Consequences of RNT in ASD

From an early age, individuals with autism exhibit atypical self-representations and cognitive inflexibility, which may increase risk for RNT and subsequent internalizing problems (De Lissnyder et al., 2012; Demeyer et al., 2012; Snyder, 2013). As young as 8 years of age, individuals with ASD endorse negative self-views and a disconnected sense of self (Burrows, Usher, Mundy, & Henderson, in press; Pfeifer et al., 2013). There is also ample evidence for reduced cognitive flexibility across development in ASD, both in laboratory assessments (Lopez et al., 2005; Panerai et al., 2014) and on self- and parent-reports (Leung & Zakzanis, 2014). Thus, when faced with self-critical thoughts or negative feedback from the environment, individuals with ASD may not be able to disengage from these thoughts. In addition, there may be consonance between their negative self-focused thoughts and existing negative views of themselves, which perpetuate RNT. In healthy individuals, negative information about oneself is in discord with positive self-views. The cognitive conflict that this discord induces often leads individuals to engage in self-regulatory strategies (Foti & Hajcak, 2010). These risk factors may interact in multiple ways to give rise to RNT in ASD.

Several recent studies support this model, identifying independent links between negative self-views, cognitive flexibility, and increased rates of anxiety and depression in children, adolescents, and adults with ASD (Boulter, Freeston, South, & Rodgers, 2013; Hollocks et al., 2014; Wallace et al., 2016; Williamson, Craig, & Slinger, 2008). However, no study to date has investigated RNT, its neural basis, or its role as a mediating factor contributing to internalizing problems in ASD.

Of specific interest for ASD, there is likely great heterogeneity in these traits across individuals, and these processes may change across development. Certain individuals with ASD may endorse positive self-views, or perseverate on topics that bring them pleasure (e.g., special interests), which likely do not confer similar risk for internalizing problems. These processes may also change from childhood to adolescence and young adulthood. During adolescence, peers become more salient to social functioning (Brown, 2004). Adolescents with ASD often experience rejection from peers (van Roekel, Scholte, & Didden, 2010), and have trouble forming stable friendships (Mazurek & Kanne, 2010). Thus, in the face of distressing experiences, adolescents with ASD likely receive less external sources of social support from friends (Picci et al., 2014). They may rely on maladaptive internal coping strategies, such as perseverating on their social difficulties. This highlights the importance of examining contributions of both individual differences in self-perceptions and cognitive flexibility, and external social factors to the development and maintenance of RNT in ASD.

No study to date has investigated neural correlates of individual differences in RNT or internalizing problems in ASD. Most studies of brain development in ASD compare groups of individuals with ASD to neurotypical individuals. Examinations of individual differences typically involve associations with autism symptom severity, ignoring the potential contributions of heterogeneity in co-occurring disorders, such as anxiety and depression. Just as in the clinical neuroimaging literature examining depression and anxiety, abnormal connectivity within and between the default mode network and salience network could contribute to increased RNT and rates of internalizing problems in ASD. Yet, the relative contribution of altered connectivity of the default mode network and salience network to RNT may differ in ASD. Perseveration on negative information about oneself could arise from hyper-connectivity of the default mode network, or impairment of salience network function resulting in difficulty appropriately directing or disengaging attention.

Studies of default mode network connectivity in ASD have been mixed in their results, with some studies finding evidence of hypo-connectivity (Burrows, Laird, & Uddin, 2016; Kennedy & Courchesne, 2008; Ypma et al., 2016), and others showing hyper-connectivity (Supekar et al., 2013; Uddin, Supekar, Lynch, et al., 2013). Still other studies find mixed connectivity profiles, possibly indicating sub-network specialization (Hahamy, Behrmann, & Malach, 2015; Lynch et al., 2013; Monk et al., 2009; Nomi & Uddin, 2015). Some inconsistencies may be due to methodological differences (Müller et al., 2011), as well as differences in participant age (Uddin, Supekar, & Menon, 2013). However, none of the previous studies account for variations in levels of internalizing problems, which could also contribute to the mixed findings. It is also possible that alternate neural mechanisms may be responsible for elevated rates of RNT in ASD than what has been observed in other clinical populations. Thus, future studies may benefit from additional control groups to determine shared or divergent mechanisms across groups.

If RNT is a product of cognitive inflexibility in ASD, then aberrant connectivity within the salience network as well as impaired coordination between the salience network and default mode network may give rise to perseverative thinking and difficulty shifting cognitive states. Connectivity within the salience network has been related to restricted and repetitive behaviors, which encompasses inflexible behavior in autism (Uddin et al., 2014; Uddin, Supekar, Lynch, et al., 2013). In addition, adolescents with ASD showed reduced activity in both the salience network and default mode network compared with TD adolescents during a social exclusion task, highlighting the joint contributions of these networks to responses to social difficulties (Masten et al., 2011). Identifying neural underpinnings of RNT in ASD has the clear potential to delineate unique and joint contributions of autism symptoms and internalizing symptoms to connectivity within and between large-scale brain networks. This may help identify individuals at risk for comorbid internalizing problems early in development.

Implications and Future Directions

In ASD, RNT may be a mechanism that links common impairments (e.g., cognitive inflexibility, social difficulties, and insistence on sameness) and heightened risk for internalizing problems. However, the dearth of studies of RNT in ASD calls for additional

empirical validation of this model. Although there is evidence suggesting that individuals with ASD exhibit heightened RNT, which confers risk for internalizing problems (Gotham et al., 2014; Matson et al., 2009; Rieffe et al., 2014), it is currently unknown whether individuals with ASD exhibit variability in the content of repetitive thoughts (e.g., repetitive positive thinking on topics of interest, repetitive negative thinking about non-self-referential topics). It will be important to examine these distinct forms of repetitive thought to uncover specific associations between repetitive *negative* self-focused thought and internalizing problems.

There may also be unexplored gender differences in these processes in ASD. Internalizing problems and their precursors (e.g., RNT) are more prevalent in females (APA, 2013; Nolen-Hoeksema, 2001), while ASD affects males at much higher rates than females (CDC, 2014). Previous research indicates that the gender differences in internalizing problems (i.e., higher rates in females) may not exist at comparable levels in individuals with ASD (Moss, Howlin, Savage, Bolton, & Rutter, 2015; Worley & Matson, 2011), though gender-related differences may also change with age (Gotham, Brunwasser, & Lord, 2015). It will be important to determine whether RNT confers similar risk for internalizing problems in males and females with ASD, as there are initial reports that these associations may be stronger for females in a typical sample (Alloy, Hamilton, Hamlat, & Abramson, 2016). There may also be gender differences in the neural mechanism underlying RNT (Ordaz et al., 2016), which should be explored further in ASD. Gender differences are rarely examined in the literature reviewed here, making it difficult to hypothesize whether the cognitive or neural mechanism for internalizing problems is comparable in males and females with ASD. Pooling data across multiple sites using publicly-available phenotypic, and neuroimaging data through data repositories such as the National Database for Autism Research (Novikova, Richman, Supekar, Barnard-Brak, & Hall, 2013) or the Autism Brain Imaging Data Exchange (Di Martino et al., 2014) may facilitate these explorations.

RNT and cognitive inflexibility are present in multiple forms of psychopathology, including anxiety, depression, obsessive-compulsive disorder (OCD), and anorexia (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Arditte et al., 2016; Britton et al., 2010; Snyder, 2013; Startup et al., 2013). Understanding RNT as a transdiagnostic vulnerability across clinical groups may help elucidate shared processes that confer risk for comorbid internalizing problems. The model we propose may further provide a foundation for subsequent studies within the Research Domain Criteria (RDoC) framework, which attempts to identify the neural basis for classes of symptoms that are present across multiple forms of psychopathology (Insel, 2014). For example, investigating an intermediate phenotype (i.e., RNT, cognitive flexibility), associated psychobiological systems (i.e., theorized neural networks), and their dimensional relationship may allow us to better understand the transmission of risk for ASD and affective comorbidity in ASD populations (Kozak & Cuthbert, 2016). A large study with a sample including multiple heterogeneous clinical groups, with measurement of factors associated with RNT at multiple levels of analysis (e.g., biological substrates, self-report) would allow comparison of associations, and identification of common or distinct patterns of deficits across various disorders. Longitudinal studies across development would also enable mechanistic examinations to help identify those at greatest risk for developing specific comorbidities. Identifying factors such as early

childhood emergence of insistence on sameness and cognitive inflexibility may help identify those at greatest risk for co-occurring impairments. Measuring these constructs at various levels of analysis (e.g., neuroimaging, self-reports, ecologically-valid lab-based assessments) may help identify the best metric for detecting early risk for internalizing problems, as assessments of RNT at different units of analysis may differentially relate to later maladaptive functioning (Lilienfeld, 2014).

Many brain structures in the executive control, salience, and default mode networks have been implicated in emotion regulation (Ochsner & Gross, 2007). This literature evolved in parallel to research examining the interactions of these three canonical brain networks at rest (Menon, 2011). Both fields of research examine the interplay of brain regions involved in emotion processing (e.g., amygdala in the salience network, ventro-medial prefrontal cortex in the default mode network), attentional control (e.g., dorso-lateral prefrontal cortex in the executive control network) and conflict monitoring (e.g. dorsal anterior cingulate cortex in the salience network). Yet, these brain regions are likely involved in multiple tasks (Mesulam, 1990; Yeo et al., 2014), and interact at rest. Task-based fMRI studies that induce RNT may also help identify the coherence between the basis for RNT during unconstrained resting states and evoked RNT. There is some initial evidence that differences in connectivity profiles between resting states and RNT are exacerbated in depressed individuals (Berman et al., 2014). However, additional research is needed to better understand the correspondence between unconstrained resting states and evoked RNT in various populations. It will be important for future research to incorporate network neuroscience and task-based approaches to better understand the contribution of these brain regions and brain networks to processes that contribute to psychopathology.

A final clinical implication is that insights about RNT in ASD may be instrumental in refining current treatment approaches. Several interventions are available that specifically target RNT, including rumination-focused cognitive behavioral therapy (Watkins, 2009). This modality focuses on changing the process of repetitively thinking about distressing self-focused thoughts, which may be a useful treatment avenue for individuals with ASD exhibiting high levels of RNT, who have insight into their thinking processes. However, this approach may not be ideal for some individuals with RNT, particularly children who may have difficulty identifying the distress caused by their thought processes. If there is support for our hypothesis that RNT is related to cognitive inflexibility, treatments focused on improving flexible problem solving may help reduce risk for and symptoms of anxiety and depression. Currently, several interventions targeting cognitive flexibility are available for children as young as 3 years of age, such as Parent-Child Interaction Therapy with Emotion Coaching (PCIT-ED; Chronis-Tuscano et al., 2009). Parent training such as PCIT-ED could help train flexible attention for children exhibiting attentional difficulties in the preschool years. Parents' support could increase the child's cognitive flexibility and emotion regulation, and offset the risk for perseverative negative self-focused thoughts in childhood and adolescence. Results from the research proposed here could translate to targeted treatment of cognitive inflexibility and negative self-referential processing.

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Figure 1.

Proposed model of interactions between self-referential processing and cognitive inflexibility underlying repetitive negative thinking (RNT) and internalizing problems. When faced with negative self-referential information, individuals with autism spectrum disorder (ASD; red arrows), may allocate attention toward self-referential processes subserved by the default mode network, and exhibit difficulties disengaging from this material due to altered connectivity of the salience network. In typical individuals (green arrows), flexible attention and top-down regulation of emotion via the executive control network may offset risk for RNT and internalizing problems.

Table 1

Summary of studies examining associations between cognitive flexibility, RNT, and internalizing problems in autism spectrum disorder (ASD).

Publication	Ages Examined	Gender and Sample Size	Cognitive Flexibility Measure	RNT Measure	Outcome	Main Findings
Crane et al., (2013)	ASD: M = 41.57, SD = 16.49; TD: M = 40.53, SD = 17.20	ASD: 28 (14 F); TD: 28 (14 F)	-	RRS Total Score	BDI-II Total score	Adults with ASD showed greater RNT and depression; strong association between the two in both the ASD and TD groups
Gillott et al., (2001)	ASD, males: M = 10.27; TD: M = 10.25; SLI: M = 10.26; Overall range = 8–12	ASD: 15 (2 F); TD: 15 (2 F); SLI: 15 (2 F)	-	SWQ, self-report	SCAS	ASD group showed higher levels of social worries than SLI or TD groups on both parent- and self-reports.
Gotham et al., (2014)	ASD: M = 20.7, SD = 3.9, Range = 16–31 years	ASD: 50 (5 F)	-	RRS Total Score	BDI-II Total Score	Levels of BDI were close to means of depressed samples, RNT was associated with higher depression symptoms.
Mazefsky et al., (2014)	ASD: M = 15.22, SD = 2.25; TD: M = 15.56, SD = 2.76; Overall range = 12–19	ASD: 25 (1 F); TD: 23 (1 F)	-	Response to Stress Questionnaire - Involuntary Engagement	YSR Internalizing problems, CBCL Internalizing problems	ASD group endorsed greater RNT, and were rated by selves and parents as exhibiting higher internalizing problems. RNT was associated with self-reported (but not parent-reported) internalizing problems in both groups.
Rieffe et al. (2011)	ASD: M = 11.42, SD = .84, Range = 9.92–12.83; TD: M = 11.52, SD = 6.25, Range = 10.25–12.91	ASD: 66 (8 F); TD: 118 (14 F)	-	Worry/Rumination Questionnaire for Children	CDI	ASD and TD groups did not differ in RNT levels. Differential associations between RNT and coping strategies were found between groups.
Rieffe et al., (2014)	ASD: M = 11.76, SD = 1.33, Range = 9.08–14.83; TD: M = 11.68, SD = 1.37, Range = 8.33–14.75	ASD: 81 (9 F); TD: 131 (72 F)	-	Worry/Rumination Questionnaire for Children	CDI	Concurrent and predictive associations between RNT and depression in ASD and TD groups.
Russell & Sofronoff, (2005)	ASD: Range = 10–13, comparison sample of TD and anxious children from previous	ASD: 65 (10 F)	-	SWQ, parent- and self-report	SCAS	Parents of children with ASD rated them as exhibiting elevated social worries, but self-

Publication	Ages Examined	Gender and Sample Size	Cognitive Flexibility Measure	RNT Measure	Outcome	Main Findings
studies						
Worley & Matson, (2011)	ASD, males: M = 8.7, SD = 3.4; ASD, females: M = 8.66, SD = 3.62; TD, males: M = 7.59, SD = 2.72; TD, females: M = 8.22, SD = 2.42; Overall range = 4–16	ASD: 70 (26 F); TD: 59 (32 F)	-	ASD-CC	ASD-CC	Parents rated that approximately 45% of children with ASD experience significant symptoms of worry. In a factor analysis, worry loaded onto the depression factor.
Hollocks et al., (2014)	ASD: M = 15.5, Range = 14.7–16.8	ASD: 90 (8 F)	Composite of Trail Making, Opposite Worlds, Numbers Backwards, and Card Sorting Tasks	-	SDQ, PONS, composites created to measure anxiety and depression	Poor executive function was associated with higher levels of anxiety, but not depression.
Lawson et al., (2015)	ASD: M = 10.07, SD = 1.77; ADHD: M = 8.93, SD = 2.69; Overall range = 6–16	ASD: 70 (7 F); ADHD 55 (16 F)	BRIEF Shift subdomain	-	CBCL Anxiety/Depression subscale	ASD group had lower flexibility than the ADHD group. Flexibility mediated group differences in anxiety/depression.
Wallace et al., (2016)	ASD: M = 21.55, SD = 4.12	ASD: 35 (4 F)	BRIEF Shift subdomain	-	ABC (Depression, Anxiety subscales)	ASD group showed impairments in flexibility and metacognition. Flexibility was negatively associated with anxiety, but not depression symptoms.

Note: sample means, standard deviations, and ranges are presented when reported by authors; M = Mean, SD = standard deviation, F = females, ASD = autism spectrum disorder, TD = typically developing, SLI = specific language impairment, ADHD = attention-deficit hyperactivity disorder, RRS = Ruminative Response Scale, BDI = Beck Depression Inventory, SWQ = Social Worries Questionnaire, SCAS = Spence Children's Anxiety Scale, BDI = Beck Depression Inventory, YSR = Youth Self-report, CBCL = Child Behavior Checklist, CDI = Children's Depression Inventory, ASD-CC = Autism Spectrum Disorders-Comorbid for Children, BRIEF = Behavior Rating Inventory of Executive Function, SDQ = Strengths and Difficulties Questionnaire, PONS = Profile of Neuropsychiatric Symptoms, ABC = Adult Behavior Checklist.