Title: Social-cognitive, physiological, and neural mechanisms underlying emotion regulation impairments: Understanding anxiety in autism spectrum disorder

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Highlights

- Anxiety in autism spectrum disorder (ASD) may stem from impaired emotion regulation.
- Emotion regulation difficulties in ASD are multiply determined.
- Targeting emotion regulation in ASD may be parsimonious and clinically effective.

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Social-cognitive, physiological, and neural mechanisms underlying emotion regulation impairments: Understanding anxiety in autism spectrum disorder

Abstract

Anxiety is one of the most common clinical problems among children, adolescents, and adults with autism spectrum disorder (ASD), yet we know little about its etiology in the context of ASD. We posit that emotion regulation (ER) impairments are a risk factor for anxiety in ASD. Specifically, we propose that one reason why anxiety disorders are so frequently comorbid with ASD is because ER impairments are ubiquitous to ASD, stemming from socio-cognitive, physiological, and neurological processes related to impaired cognitive control, regulatory processes, and arousal. In this review, we offer a developmental model of how ER impairments may arise in ASD, and when (moderating influences) and how (meditational mechanisms) they result in anxiety.

Emotion regulation (ER) refers to the ability to modulate experienced and expressed emotion in the service of goal-directed or value-based behavior. For example, becoming transiently angry when someone takes your parking space may be a normative response, but it is not adaptive to act on that anger in an aggressive manner. In such situations, optimal ER skills allow for the down-regulation of negative emotions to proceed with the task at hand (i.e., find another place to park). An impoverished ability to cope with and control intense, especially negative, emotions is associated with a range of psychiatric conditions and symptoms (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Berking et al., 2012; Berking & Wupperman, 2012), and the goal of this review is to explore ER impairment in relation to manifest anxiety in autism spectrum disorder (ASD).

Over the last several years, there has been burgeoning scientific interest in the possibility that ER impairments are nearly ubiquitous in ASD (Mazefsky et al., 2013). Impaired ER may underlie many of the behavior problems commonly seen in children and adults with ASD, such as aggression, irritability, and anxiety (Mazefsky & White, 2013). Anxiety is among the most commonly observed and impairing associated (i.e., non-core) symptoms in ASD (e.g., White, Oswald, Ollendick, & Scahill, 2009). As many as four out of five children with ASD are diagnosed with comorbid psychiatric disorders (Simonoff et al., 2008) and, although there is evidence that diagnostic practices that take into account the ASD-related impairments would result in fewer comorbid diagnoses (Mazefsky, Oswald, Day, Eack, Minshew, & Lainhart, 2012), children, adolescents, and adults with ASD are clearly at increased risk of experiencing a range of secondary behavioral and emotional problems.

In this review, we consider socio-cognitive, physiological, and neural mechanisms that may serve as mediators of ER impairments in ASD. We then explore possible pathways between disrupted ER and the behavioral manifestations of anxiety in ASD, with a focus on intra-individual moderating influences. The goals of this paper are to synthesize the extant literature related to specific processes involved in ER impairments in ASD and to identify factors that may cause ER deficits to manifest as anxiety. We conclude with recommendations for future research to systematically evaluate the plasticity of ER mechanisms and thereby reduce anxiety in ASD.

Overview: Emotion Regulation and Anxiety in ASD

Anxiety is an emotional response with both affective and physiologic components. Anxiety can be defined as nervous tension and autonomic arousal, often accompanied by general distress (Clark & Watson, 1991). The *regulation* of emotion is distinct from the *experience* of that emotion. For example, a child might cope with anxiety about speaking in front of peers by reminding himself that most other children his age also get anxious or by feigning illness on the morning of a class presentation. Reappraisal and avoidance behaviors such as these are strategies to modulate or regulate the emotion responses. Emotional experience is automatic and often intense, whereas the regulatory strategies used for coping with the situation are often explicit and intentional.

ER is a broad, multilevel process, involving inter-related systems (e.g., attention, physiology, neurological processes; e.g., Calkins, 2010). Regulatory strategies are typically used to increase, or heighten, an emotional experience (up-regulation), decrease the emotion itself, or dampen the outward expression of the emotion (down-regulation). Derived from Gross' (2001) process model of ER, strategies can also be categorized in relation to emotional experience. Regulation can occur prior to the experience of the emotion or in response to the emotion,

termed antecedent-focused and response-focused strategies, respectively. For example, avoidance of situations likely to trigger an unpleasant emotion is an antecedent strategy whereas suppression of an emotion is response-focused and occurs after the emotion generating experience. Additionally, some regulatory strategies are explicit and intentional (e.g., reappraisal, suppression), whereas others are implicit, or occurring without conscious intention (e.g., affect labeling; Gyurak, Gross, & Etkin, 2011).

A person's 'regulatory style' is associated with general well-being (Gross & John, 2003) and, in some cases, the development of psychopathology (Ciccetti, Ackerman, & Izard, 1995). Developmentally, regulatory ability improves dramatically during the first few years of life (Calkins, 2010) and is predictive of positive outcomes. A child's ability to effectively manage emotions, for example, predicts better adaptive behavior and social relationships (Eisenberg & Fabes, 2006). People who consistently engage in adaptive cognitive reappraisal tend to have stable, close interpersonal relationships and more positive emotions than do people who do not readily engage in reappraisal. Those who habitually suppress emotion, on the other hand, experience more negative affect and often experience inauthenticity, or a sense of externally presenting a false persona (Gross & John, 2003).

Emotion dysregulation is a transdiagnostic risk factor (i.e., a fundamental process underlying multiple disorders or symptoms) for psychopathology. In the developmental psychopathology literature, for example, there is a strong association between ER impairments and development of internalizing problems, such as anxiety and depression (e.g., Southam-Gerow & Kendall, 2000). McLaughlin and colleagues (2011) demonstrated, in one of the few longitudinal studies in the field, that ER deficits prospectively predicted not only changes in

adolescents' anxiety but also aggressive behavior and eating pathology. Conversely, psychopathology did not predict subsequent ER deficits.

Although there is little empirical research on ER in ASD, there has been considerable study of the experience and expression of emotion in ASD. This research has demonstrated that people with ASD often have poorly differentiated emotional responses and self-knowledge, tend to experience more negative emotion, and are harder to soothe once aroused, relative to peers without ASD (e.g., Konstantareas & Stewart, 2006). From infancy through adulthood, individuals with ASD are often described as having low levels of positive affect along with heightened negative affect and dysregulated behavior, compared to peers without ASD (Garon et al., 2009; Mazefsky, Pelphrey, & Dahl, 2012). Children with ASD, when frustrated, display more intense and prolonged periods of resignation (i.e., giving up) and less effective ER strategies (e.g., more avoidance) compared to typical peers (Jahromi, Meek, & Ober-Reynolds, 2012). They tend to show poor emotional insight and struggle to adequately express emotion via verbalization, facial expression, or other nonverbal means (e.g., Losh & Capps, 2006).

Our goal is to offer an evidence-informed heuristic for understanding ER impairments as a risk factor that may manifest as anxiety in people with ASD. Among psychiatric comorbidities seen in ASD, anxiety disorders are the most common (deBruin, Ferdinand, Meester, de Nijs, & Verheij, 2007; Joshi et al., 2010; White et al., 2009), affecting about 40% of children and adolescents with ASD (van Steensel, Bogels, & Perrin, 2011). As noted above, we propose that ER impairments, through a host of biological and nonbiological mechanisms, are fundamentally related to ASD. In this model, ER impairment is viewed as a transdiagnostic risk factor affected by multiple mechanisms, which are etiologically linked to ASD (i.e., equifinality), whereas anxiety is only one possible, though likely, outcome of impaired ER in ASD (i.e., multifinality).

Most clinical affective neuroscience research has focused on emotions as discrete categories, where each emotion is thought to emerge from independent neurobiological systems (for a review, see Posner, Russell, & Peterson, 2005), and this approach has yielded important advances in the understanding of neurobiological mechanisms of affect. However, there is strong evidence that discrete emotion categories are constructed of more general brain networks, suggestive of a dimensional model that conceptualizes that all affective states arise from common, overlapping neurophysiological systems (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012). Dimensional models of affect have a long history in psychological research (Russell, 2003) including the circumplex model of affect that proposes that all affective states arise from two fundamental neurobiological systems defined by the near-orthogonal dimensions of valence (i.e., pleasure-displeasure) and arousal (i.e., alertness or vigor; Russell, 1980). This framework suggests that every emotion may be represented on the basis of varying degrees of valence and arousal. For example, feeling tense is the product of a negatively valenced and highly aroused emotional state; whereas feeling serene is the product of a positively valenced and low arousal state.

The circumplex model of affect suggests that dysregulated arousal systems would have a direct impact on the experience of all emotions, and Tseng and colleagues (2013) recently found that a circumplex model of experienced affect is characteristic of individuals with ASD. One potential mechanistic account for impaired ER, and the resultant increased anxiety, in ASD is that individuals on the spectrum may experience heightened levels of basal or reactive arousal. Arousal is regulated by connections between the reticular formation in the brainstem and the limbic system, including the amygdala, and the thalamus and parietal lobes (Heilman, 2000), and there is evidence of impairments in functional and structural connectivity between the brainstem

and limbic system in ASD (Elison et al., 2013; Fatemi, et al., 2012). Additionally, a comprehensive functional neuroimaging literature implicates impaired processing of emotional stimuli in ASD (for a review, see Dichter, 2012). To the extent that arousal systems may be dysregulated in ASD, this would have a direct influence on the experience of affective states, potentially contributing to impaired ER in ASD.

In addition to neural and physiological mechanisms that affect regulatory capacity, there are cognitive and social processes that influence the experience of, and ability to intentionally alter, emotion. In typical development, ER emerges rapidly, largely through interactions between the child and parent. Just as altered interactions between a child (or infant) and the social environment can affect, and be affected by, the child's temperament (Dawson, 2008), this interaction can also affect ER development. In the following sections, we explore these broad domains of mediational mechanisms – socio-cognitive, neural, and physiological, as they relate to understanding impaired ER in people with ASD.

Socio-Cognitive Mechanisms

Recognition, Expression, and Socialization of Emotion

Familial socialization of appropriate emotional responding, often referred to as emotion coaching, plays a critical role in the development of ER in non-ASD populations (e.g., Dunsmore, Booker, & Ollendick, 2013). Theoretical models, supported by a wealth of research, indicate that young children develop ER skills through observational learning, modeling, and social referencing (Morris, Silk, Steinberg, Myers, & Robinson, 2007). This is largely a spontaneous process that happens through family interactions without explicit instruction or directive teaching for most children. However, child characteristics can moderate this process

(Morris et al., 2007), and the prominent social deficits in ASD may interfere with the observational learning of ER in early childhood.

Whereas typically developing infants demonstrate a natural preference for others' faces, early development in ASD is characterized by reduced social attention and motivation (e.g., Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998), and diminished salience and abnormal perception of social cues, based on eye-tracking and electrophysiological studies (Dawson, Webb, & McPartland, 2007). Further, attention to others' eyes may decline by 6 months of age in infants later diagnosed with ASD (Jones & Klin, 2013). This suggests that reduced social interest is evident by the time young children who later develop ASD *should be* vicariously learning foundational ER skills from their interactions with others (e.g., parents, siblings). Given the interdependence of social and emotional development, it is not surprising that individuals with ASD present with ER impairments.

One of the fundamental ER skills acquired early in development is emotion recognition. Competence in interpersonal situations is highly dependent on awareness of one's own emotions and those of others (Saarni, 1999). Accuracy in emotion recognition is requisite for higher level emotional and social understanding (Jones et al., 2011). Difficulty recognizing, and especially labeling, emotions in self and others may directly and indirectly impede effective ER. Tupak and colleagues (2014) found that affect labeling was associated with activation of the ventrolateral prefrontal cortex (VLPFC) in a healthy population. These findings suggest that an inability to recognize and label emotions could lead to under-activation of neural regions directly involved in implicit ER. Indirectly, misperception or misinterpretation of emotional signals could hamper ER.

Findings from research on emotion recognition deficits in ASD are quite mixed (e.g., Harms, Martin, & Wallace, 2010; Jones et al., 2011). Kennedy and Adolphs (2012), for example, found that adults with ASD demonstrated decreased sensitivity in emotion perception relative to non-affected adults. Likewise, Tanaka and colleagues (2012) reported decreased ability to generalize facial emotions across identities. On the other hand, Ozonoff and colleagues (1990) found that although children with ASD displayed some deficits in emotion perception relative to non-affected controls, the deficits were not seen uniformly across experimental tasks and were not present when the control children were matched to those with ASD on verbal ability.

Although the existence of a global and pervasive deficit in emotion recognition in ASD has not been firmly established, Uljarevic and Hamilton (2013) reported results from a meta-analysis of 48 emotion recognition studies representing data from over 980 participants with ASD, indicating that 'basic' emotions (anger, sadness, surprise, fear, disgust) were recognized less accurately in ASD, with the exception of happiness, which appeared to be (marginally) intact overall. Interestingly, neither age nor IQ moderated this effect, suggesting that although the effect may not be truly global (due to apparently preserved recognition of happiness), the mixed results may be due to the dramatic heterogeneity in tasks used to measure this process (e.g. emotion-labeling tasks, emotion-matching tasks) as well as heterogeneity in the participant groups involved in these studies. Despite these inconsistencies, it can be concluded that more demanding tasks with subtle stimuli are most challenging, there are some emotion-specific difficulties (e.g., fear and sadness; Tell, Davidson, & Camras, 2014), and people with ASD improve developmentally in this skill but never reach typical adult proficiency (Rump, Giovannelli, Minshew, & Strauss, 2009).

Although the exact nature of emotion recognition deficits in ASD is not resolved, it is generally agreed that the manner in which emotional expression is processed and interpreted is atypical in ASD. Research in both children and adults suggests that individuals with ASD are more likely than typically-developing individuals to interpret ambiguous or neutral faces as negative, suggesting a possible bias (Eack, Mazefsky, & Minshew, 2014; Kuusikko et al., 2009). Moreover, neuroimaging and eye-tracking research has generally found differences between people with and without ASD, across metrics, on emotion recognition tasks even when performance deficits are not found (see Harms et al., 2010 for review), which suggests engagement of compensatory approaches for emotion recognition. One such compensatory strategy may be application of a rule-based approach (e.g., smile indicates happiness) to emotion interpretation, rather than the more typical application of a 'prototype' of a given emotion (Walsh et al., 2014). Prior eye-tracking research has indeed found differences in the visual scanpaths of people with ASD when viewing emotional faces (Gross, 2004; Klin, Jones, Schultz, Volkmar, & Cohen 2002). This line of reasoning was first suggested based on failure to find an inversion effect in ASD, which involves slowed facial identification when a face is presented upside down (see Sasson, 2006 for review). In further support of this, Tanaka et al. (2012) reported a tendency to process facial features as isolated, non-integrated parts within a sample of children, adolescents, and adults with ASD. Additionally, affect-matching paradigms tend to result in more sizeable group differences in facial emotion recognition ability than do affect labeling paradigms (e.g., Davies et al., 1994; Piggot et al., 2004; Rump et al., 2009). This suggests that more cognitively and verbally able individuals with ASD might engage less automatic cognitive and linguistic strategies to decode emotions than typically developing individuals (Harms et al., 2010).

Compared with research on the perception of emotion in others, there has been less work on the ability of people with ASD to recognize and express their own affect. There is, however, evidence for impaired access to and expression of consciously felt emotion (Shalom et al., 2006). Children with ASD smile less often and tend to not show self-conscious affect, relative to children without ASD (Dawson & McKissick, 1984; Mundy & Sigman, 1989; Spiker & Ricks, 1984). Finally, difficulty in identifying, distinguishing, and describing one's own emotions (often referred to alexithymia) has been documented in ASD samples (e.g., Rieffe, Terwogt, & Kotronopoulou, 2007). These impairments may interfere with successful ER in ASD given that the capacity to label, and communicate about, one's own emotions are essential aspects of effortful ER (Mazefsky & White, 2013).

Attention, Working Memory, and Cognitive Control

Monitoring and altering the course of emotional experience requires attentional and cognitive processes. There has been a wealth of research on cognitive processes in ASD, including research on attention, working memory, and information processing. Although this research has rarely explicitly focused on how differences in these cognitive processes impact emotional functioning in ASD, research in typically developing samples and other clinical populations has established the importance of higher order cognitive processes and executive functions in ER (Ochsner & Gross, 2005; Zelanzo & Cunningham, 2007). Below we consider how understanding cognitive functioning in ASD may inform the understanding of observed ER deficits in ASD.

Effective ER is characterized by adaptive, goal-directed behavior, which requires the integration of multiple components of executive function. For example, internal goal representations must be kept in awareness while inhibiting interfering cognitions and behaviors

(Solomon, Ozonoff, Cummings, & Carter, 2008). Cognitive control refers to the ability to reallocate mental resources in the service of values and goals. Key components of cognitive control related to ER include attentional control and controlled cognitive change (Ochsner & Gross, 2005). For example, an adaptive response may require limiting attention to a negative stimulus and focusing attention on salient aspects of the context to arrive at the most appropriate response. Flexible, integrated cognitive responses are required to generate or regulate an emotion.

Impairments in cognitive flexibility and the ability to shift attentional focus have been well-documented in ASD (Hill, 2008; Ozonoff, Coon, Dawson, Joseph, Klin, & McMahon, 2004; Ozonoff & Strayer, 1997; Rinehart, Bradshaw, Moss, Brereton, & Tonge, 2001). This has been demonstrated as a tendency to perseverate, or cogitate on one thought or task to the exclusion of other thoughts and behaviors. Perseveration is a clinical concern because such focused attention impedes appropriate task switching. Problems with shifting attention are also observed in the form of difficulty disengaging attention to perform a task (e.g., Landry & Bryson, 2004). The tendency to hyper-focus on aspects of a situation at the exclusion of other, potentially more relevant, signals extends beyond perceptual processes (Ozonoff, Strayer, McMahon, & Filloux, 1994) to a problem with higher-order demands for conceptual integration.

Manifest difficulties with cognitive rigidity can be couched in the theory of Weak Central Coherence (WCC; Frith, 1989; Frith & Happé, 1994), which holds that individuals with ASD have relative strengths in local processing and may lack the automatic drive to integrate stimuli to make global meaning of context. The information processing approach of people with ASD is often piecemeal and detail-oriented, regardless of salience or meaning of the gestalt. This may

also present as over-reliance on specific responses or scripts, even when such behaviors are not ideal for the situational demands.

Inflexibility can also reflect difficulty inhibiting a response that interferes with goal-directed behavior. In a cross-sectional study, Ozonoff et al. (2004) found that adolescents with ASD made more errors than typically developing adolescents on a task requiring inhibition of prepotent responses compared with children under the age of 12. In addition, adolescents with ASD made more errors than did younger children with ASD, suggestive of a lack of age-related improvement during adolescence in ASD.

Problems with the conceptual integration of information in ASD can result in a host of cascading and reciprocal effects on behaviors with relevance to ER, including difficulty with perspective-taking, an inability to think hypothetically, and an impaired ability to develop novel behavioral solutions to problems (Dunlop, Knott, & MacKay, 2008; Hill, 2008; Pugliese & White, 2014; Reed & Peterson, 1990). For example, set-shifting difficulties may also be related to the inability to recognize that one's solution is faulty (Perner, 1998). Arguably, most situations that demand regulation of emotion in daily life are not planned, lack clear rules for how to best handle the situation, and require disengagement from the emotional trigger. Cognitive perseveration, along with deficits in perspective-taking, may contribute to the inability to see more than one side of a situation (making reappraisal difficult) and contribute to emotional rumination, collectively leading to impaired ER.

Summary

The rich research on the maturation of ER abilities in typically developing children can shed light on how ER impairments arise in ASD. From very early in life, caregivers play a considerable role in helping the young child self-regulate emotion (e.g., Rothbart & Bates, 2006).

As the child's inhibitory control, attention, and ability to self-soothe improve, parental control over the child's regulation is gradually scaffolded (Eisenberg & Sulik, 2012). In ASD, normative social orienting (e.g., child attending to parent) is derailed early in development (Dawson, 2008; Jones & Klin, 2013). There are often deficits in cognitive control, flexibility, and problem-solving (e.g., Ozonoff et al., 1994; Rinehart et al., 2001), all higher order skills involved in ER. Although the research has been mixed, there is evidence too of deficits in foundational skills for ER, such as emotion awareness, recognition, and accurate expression (e.g., Eack et al., 2014; Harms et al., 2010; Rieffe et al., 2007). As such, the development of ER ability may be hindered in ASD, via processes related to wayward socialization, impaired executive function, and fairly rudimentary emotion awareness and recognition skills.

Physiological Mechanisms

The idea that ASD is a disorder of irregular resting-state physiology dates back to Hutt and colleagues (1964), who suggested that those with ASD have a ''chronically high state of arousal'' (p. 908), and is now supported by multiple lines of evidence suggesting that ASD is characterized by altered levels of basal and reactive arousal. One indirect line of evidence is the well-documented finding that individuals with ASD gaze less at the eye regions of images of faces (Kliemann, Dziobek, Hatri, Steimke, & Heekeren, 2010; Klin et al., 2002; Pelphrey, et al., 2002), a pattern that has been suggested to reflect a state of over-arousal (Levine et al., 2012; Riby, Whittle, & Doherty-Sneddon, 2012) linked to hyperactive amygdala activation when looking at the eye regions of the face (Dalton et al., 2005). Below, we describe some of the most prominent approaches utilized in physiological research on emotion processes and their application to understanding ASD.

Startle Responses

A number of studies have suggested differences in basal states of arousal on the basis of altered magnitudes of the startle eyeblink response. The startle eyeblink response is an obligatory reflex elicited by a startling probe, the magnitude of which is modulated by internal states of arousal, attention, and valence (Bradley, Codispoti, Cuthbert, & Lang, 2001; Lang & Davis, 2006). Fear-potentiation of the startle response is mediated by projections from the central nucleus of the amygdala (Hitchcock & Davis, 1991), and there is a large literature documenting altered fear-potentiated startle responses in anxiety disorders (Lang, Davis, & Ohman, 2000). Although Sterling and colleagues (2013) reported normal threat-potentiated startle responses in adolescents with ASD and found that startle responses did not predict levels of anxiety or social impairments, Chamberlain and colleagues (2013) reported greater absolute startle responsivity at baseline and throughout a threat-potentiated startle experiment in adolescents with ASD, despite no differences in startle modulation due to cued or uncued threat, suggesting context-general enhanced arousal in threatening contexts.

Modulation of the startle response may be measured in the context of both pleasant and unpleasant stimuli, and the degree of startle attenuation in appetitive contexts and augmentation in withdrawal contexts (i.e., affective modulation of the startle response) is known to reflect both the arousal and valence properties of the contextual affective stimuli (Lang, Bradley, & Cuthbert, 1998). Studies of affective modulation of the startle response in ASD have found evidence of startle eyeblink magnitude potentiation while viewing pleasant normative images, despite no differences in affective ratings of images relative to subjects without ASD (Dichter, Benning, Holtzclaw, & Bodfish, 2010; Wilbarger, McIntosh, & Winkielman, 2009) as well as potentiation while viewing pleasant social images (Cohen, Masyn, Mastergeorge, & Hessl, 2013). Wilbarger and colleagues (2009) also reported intact implicit valence responses, reflected in facial

electromyography (EMG), suggesting that aberrant startle eyeblink responses to pleasant pictures may reflect impaired processing of picture arousal rather than valence. In addition, Dichter and colleagues (2010) found evidence of impaired startle-induced postauricular modulation in the context of unpleasant pictures, further suggesting that patterns of altered startle responses are not due to picture valence, but instead more likely picture arousal, in contexts where startle reflexes should be attenuated but rather are amplified. Finally, Mathersul and colleagues (2013) found no differences in startle modulation or electromyography activity (i.e., orbicularis, zygomaticus, corrugator) in adults with ASD to normative neutral, pleasant, and unpleasant images, though this study used extremely intense images (e.g., erotica and mutilation) which may have elicited more normative responses. In summary, available startle eyeblink modulation data suggests mixed evidence of enhanced fear-potentiated startle, but more consistent evidence of startle potentiation in positive affective contexts likely linked to processing the arousing properties of affective images. Though more research is needed, this pattern suggests that altered states of arousal in ASD may impact processing of arousing positive stimuli, including images of faces.

Skin Conductance Responses

The skin conductance response (SCR; electrodermal activity) is a psychophysiological index of autonomic arousal, reflecting an orienting response that is elicited by salient environmental stimuli (particularly socially relevant information) (Critchley, 2002; Sequeira, Hot, Silvert, & Delplanque, 2009). It mobilizes physiologic resources to facilitate behavioral responses and reflects arousal and motivation (Lang, 1995). Research into autonomic responsivity, as measured by SCRs in ASD, is highly inconsistent and does not clearly indicate altered states of autonomic arousal in ASD. A number of SCR studies have found evidence of hyper-arousal in children and adolescents with ASD. van Engeland and colleagues (1991)

reported larger SCRs to novel stimuli but normalized SCR when subjective, idiosyncratically arousing stimuli were added to the novel stimuli. Kylliainen and Hietanen (2006) reported higher SCRs to socially-relevant stimuli in children with ASD, and Joseph and colleagues (2008) reported relatively larger SCRs in children with ASD to face images with direct and averted gaze. Hirstein and colleagues (2001) reported that children with ASD did not show a larger SCR to images of their mother versus an image of a cup. Finally, Cohen and colleagues (2013) reported that adolescents with ASD and with ASD plus Fragile X had larger SCRs than controls while viewing pleasant and unpleasant pictures, reflective of a general state of hyper-arousal.

However, research on atypical SCRs in people with ASD has not consistently been suggestive of hyper-arousal. Indeed, a number of studies have found lower SCRs in ASD. Hubert and colleagues (2009) reported lower SCRs in adults with ASD during an emotional face judgment task. Mathersul and colleagues (2013) found an overall dampening of SCRs to socially pleasant, but not neutral, images in adults with ASD. This was interpreted as a failure to orient to socially relevant stimuli and a greater relative allocation of attention to neutral images. This study also reported decreased evoked cardiac acceleration (ECA) to social pleasant images, suggesting reduced perceived motivational intensity of these images, yet no differences in evoked cardiac deceleration (ECD) to any image category. The authors interpreted these findings to reflect intact initial automatic orienting to affective stimuli (reflected in the ECD response) but that this attentional allocation fails to sustain over time, reflected in dampening of SCRs. Finally, Riby and colleagues (2012) found lower SCRs in individuals with ASD relative to controls and to participants with Williams Syndrome, and did not show physiological reactivity differentiation between groups to happy, sad, and neutral live and video faces, suggestive of decreased arousal across social contexts. Kushki and colleagues (2013) reported

elevated SCRs while watching a neutral movie but blunted SCRs during an anxiety-provoking Stroop task (and elevated heart rate during both conditions) in children with ASD, suggesting context-specific and perhaps paradoxical autonomic system dysfunction in contexts eliciting anxiety (i.e., a larger SCR at baseline but smaller SCR during a task meant to elicit anxiety).

Finally, Shalom and colleagues (2006) found no differences in SCRs to pleasant, neutral, and unpleasant images between children with ASD and controls despite divergent affective ratings of the images, and Louwerse and colleagues (2014) found no group differences in SCRs, heart rate, or subjective responses to social and nonsocial affective image in adolescents with an ASD. Blair (1999) reported no differences in SCRs to distressing, threatening, or neutral stimuli in children with ASD, indicative of intact autonomic and subjective responses to stimuli with and without a social content. South and colleagues (2011) recorded SCR during a simple discrimination conditioning task in children and adolescents with and without ASD and found no differences in baseline SCRs or group differences in SCRs to conditioned stimuli. However, they found that SCRs to conditioned fear stimuli in the ASD group was associated with symptoms of social anxiety (positive association) and social functioning (negative association).

Cardiovascular Activity

Respiratory sinus arrhythmia (RSA) is a measure of heart rate variability related to breathing that is influenced by the parasympathetic branch of the autonomic nervous system. The amplitude of RSA is widely applied as an index of the myelinated vagus function or cardiac vagal tone (Berntson, Cacioppo, & Grossman, 2007; Grossman & Taylor, 2007). Vagal tone, RSA, and other measures of heart rate may be useful metrics for understanding parasympathetic responses to stress related to ER (Porges, Doussard-Roosevelt, & Maiti, 1994). The interpretation of RSA is dependent on state, with different expectations for resting state versus

change-related measures (Mazefsky et al., 2013). Polyvagal theory proposes that higher baseline RSA is associated with better social interaction and ER, whereas low levels, as well as unreliable RSA modulation, confer risk for problems in these areas (Porges, 2007). This theory has been widely supported, with high frequency heart rate and reduced vagal control (as measured by RSA) found in populations with anxiety or depression (Licht et al., 2009; Rottenberg, 2007).

Consistent with Polyvagal Theory, there is some research supporting a link between higher baseline RSA amplitudes and better social behavior in ASD (Patriquin, Scarpa, Friedman, & Porges, 2013). Along the same lines, Klusek and colleagues (2013) reported dampened vagal tone in boys with ASD that was correlated with pragmatic (i.e., social) language impairments. These findings are consistent with research indicating low parasympathetic activity, including lower heart rate variability, at rest in ASD (Cohen et al., 2013; Ming et al., 2005). On the other hand, research investigating the relationship between RSA and vagal tone modulation and ER-related concepts in ASD is quite limited and findings are mixed. Levine et al. (2012) found no difference in vagal tone responses to stress between participants with ASD and typical controls. Conversely, a study of 14 children with ASD found lower baseline levels of RSA, lower heart rate variability, and higher heart rates, reflective of decreased parasympathetic nervous system activity, compared to typically developing controls (Guy, Souders, Bradstreet, DeLussey, & Herrington, 2014). Further, decreased RSA was associated with more severe parent-reported anxiety symptoms (Guy et al., 2014). Similarly, Moskowitz et al (2013) found that lower-functioning children with ASD had higher heart rates and lower RSA in high versus low anxiety conditions. These two studies suggest lower baseline levels of RSA in ASD, as well as an association between resting RSA and anxiety. Although one might also expect poorly modulated RSA in ASD, more research is needed to determine whether or not this is uniformly the case.

Pupillometry

Pupillometry involves the measurement of changes in pupil diameter, to index the intensity of mental activity and changes in attention and perception (Laeng, Sirois, & Gredebäck, 2012). Given its noninvasive nature, this metric has grown more popular as a general measure of overall brain activity or emotional reactivity. Nuske and colleagues (2014) reported no differences in resting-state (tonic) pupil size in children with ASD, although two studies (Anderson & Colombo, 2009; Anderson, Colombo, & Unruh, 2013) reported larger tonic pupil sizes, indicative of hyperarousal, in young children with ASD. Martineau and colleagues (2011) also found a difference, but in the opposite direction. Specifically, they reported smaller mean pupil size in children with ASD while viewing neutral faces, virtual faces, and objects. Fan and colleagues (2009) reported that children with ASD had longer transient pupillary light reflex (PLR) latency, smaller constriction amplitude and lower constriction velocity than children with typical development. In sum, although the majority of pupillometry studies in ASD have found differences compared to typically-developing children, the type of differences and direction of effects have been variable. Additional research is needed to better understand how pupillometry measures differ in ASD, including consideration of the impact of within group heterogeneity (particularly related to ER) on pupilometry indices.

Salivary Cortisol

Hydrocortisone, usually referred to as cortisol, is a steroid hormone that is excreted during or after stress in humans as part of the systematic arousal of the HPA axis (Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2013). Whereas some studies of cortisol in ASD have suggested chronic cortisol over-responsiveness (e.g., Bitsika, Sharpley, Sweeney, & McFarlane, 2014), others have found a blunted or decreased cortisol response (Levine et al., 2012). Wide

variability in cortisol levels between children with ASD has been reported (Corbett, Schupp, Levine, & Mendoza, 2009). Among non-ASD samples, large intraindividual variability exists as well, with genetics, gender, and smoking noted as some key contributors to this variability (see Kirschbaum & Hellhammer, 1994 for review). The degree of social impairment appears to play a role in cortisol levels in ASD, with lower cortisol levels associated with more social motivation (Corbett et al., 2013).

There is also a well-established relationship between cortisol levels and stress responses in the non-ASD literature (see Dickerson & Kemeny, 2004 for review). Research on cortisol levels in samples with clinical anxiety varies across the specific disorder studied, though most often there is a reduction in cortisol levels with effective treatment (see Elnazer & Baldwin, 2014 for review). One would expect that degree of emotion dysregulation and anxiety may also drive cortisol differences in ASD. Indeed, there is some support for higher peak cortisol and prolonged duration and recovery of cortisol elevation in children with ASD after a stressful experience (e.g., blood draw; Spratt et. al, 2011). One might similarly expect the degree of anxiety in ASD to correspond with cortisol levels; however, one small study found no relationship between self-reported anxiety and salivary cortisol in children with ASD (Simon & Corbett, 2013).

Summary

In summary, the literature addressing physiological measures of arousal in ASD, though mixed, is generally supportive of altered states of basal and reactive arousal. Evidence of larger startle responsivity at baseline, in threatening contexts, and while processing positive and social stimuli is suggestive of heightened states of arousal in ASD. The literature on SCRs in ASD is particularly mixed, with evidence of unimpaired, larger, and smaller reactivity, but the preponderance of studies support altered SCRs, suggesting a failure to orient appropriately to

both social and nonsocial environmental stimuli. There is also support for low parasympathetic activity at rest in ASD, as indicated by relatively low baseline RSA and vagal tone, a pattern that is typically associated with greater social and emotional impairment (Porges, 1997). Studies utilizing both pupillometry and cortisol measures in ASD generally report differences compared to typically-developing controls, though the direction of effects is variable. Given the ability of many of these these physiologic measures of arousal to index very rapid responses to the environment (i.e., on the order of milliseconds), these data suggest altered orienting to the environment very early in the stream of information processing in ASD.

Neural Mechanisms

Neural Substrates of ER in Non-Clinical participants

We first review the extensive literature on the neural mechanisms of ER in non-clinical participants (Beauregard, Levesque, & Bourgouin, 2001; Blair et al., 2007; Kim & Hamann, 2007; Ochsner & Gross, 2005; Phan et al., 2005) prior to discussing neural substrates of impaired ER in ASD. The majority of these studies has assessed the neural substrates of explicit ER strategies, with a particular focus on cognitive reappraisal, which involves reinterpreting an emotion-eliciting stimulus to consciously change one's emotional response (Ochsner and Gross, 2005; though see Etkin et al., 2009, 2010 for studies of implicit ER). Increasingly, these data suggest that consciously deployed attempts to alter an emotional experience are mediated via effects of prefrontal cortex (PFC) on limbic regions that alter experiential, behavioral, and neurobiological aspects of emotional responses (Dillon & Labar, 2005; Eipprt et al., 2007; Gross, 1998; Jackson, Malmstadt, Larson, & Davidson, 2000; Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Ray, McRae, Ochsner, & Gross, 2010; Urry et al., 2006). Specifically, conscious changes in emotional responses are brought about by dorsolateral, ventrolateral, and

medial PFC regions involved in cognitive control as well as by subcortical regions involved in arousal and motivation, including limbic and brainstem regions and medial and orbitofrontal prefrontal cortices (Critchley, 2005; Dolan, 2002; Johnstone et al., 2007) and the interplay among these areas (Derryberry & Rothbart, 1997; Urry et al., 2006).

Medial PFC (mPFC) has been linked to the regulation of amygdala and other cortico-limbic activity (Phelps, Delgado, Nearing, & LeDoux, 2004; Quirk, Likhtik, Pelletier, & Pare, 2003) and varies with the direction of regulation (Eippert et al., 2007; Harenski & Hamann, 2006; McRae et al., 2010; Ochsner, Bunge, Gross, & Gabrieli, 2002; Ohira et al., 2006; Schaefer et al., 2002). Specifically, cognitive strategies that down-regulate responses to aversive stimuli recruit dorsal and ventral prefrontal cognitive control regions, including dorsal, lateral, and medial PFC, and anterior cingulate cortex, while simultaneously reducing activation in areas associated with emotion processing, including the amygdala, medial and lateral OFC, and nucleus accumbens (Kalisch, 2009; Kim & Hamann, 2007; Levesque et al., 2003; Ochsner et al., 2002; Ochsner et al., 2004; Phan et al., 2005). Reductions in negative affect predict lateral and medial PFC activation (Ochsner et al., 2002; Phan et al., 2005) and negatively correlate with amygdala activation (Ochsner et al., 2004; Phan et al., 2005). This pattern highlights an important relationship between emotion and cognition in ER contexts, such that dorsal cognitive abilities modulate ventral affective responses (Ayduk, Mischel, & Downey, 2002).

Largely overlapping PFC regions mediate intentional attempts to change positive emotional responses (Kim & Hamann, 2007); however the corresponding activation of limbic regions, including the amygdala and nucleus accumbens, is increased (Heller et al., 2009; Ochsner et al., 2004) suggesting that cognitive control affects both the up- and down-regulation of emotion and depends on the valence of the ER target. The degree of success of reappraisal has

also been correlated with activity in regions of PFC (Eippert et al., 2007; Kober et al., 2008; Levesque et al., 2003; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008), anterior cingulate cortex (Phan et al., 2005), and amygdala (Eippert et al., 2007; Phan et al., 2005), and with the degree of correlation between the amygdala and mPFC (Banks, Eddy, Angstadt, Nathan, & Phan, 2007). Thus, top-down regulatory projections from PFC modulate limbic activity in response to emotional stimuli, forming a frontolimbic circuit of ER (Bishop, Duncan, Brett, & Lawrence, 2004; Ochsner et al., 2005; Urry et al., 2006).

Neural Substrates of Emotion Processing in ASD

Despite the increasing evidence that ER impairments play a key role in ASD, studies examining the neural mechanisms of ER in individuals with the disorder are rare. However, a growing literature points to neural anomalies during emotion processing that may underlie ER impairments in ASD. These studies have focused largely on neural functioning in the socio-affective domain (e.g., Alaerts et al., 2011). Neuroimaging studies examining incidental socio-emotional processing have often used a facial identification task in which participants are asked to identify the gender of emotional faces; participants with ASD typically do not differ from non-psychiatric controls in behavioral accuracy when identifying gender (e.g., Spencer et al., 2011). In a large study using this task in individuals with ASD, their unaffected siblings, and matched controls, Spencer et al. (2011) reported reduced activity in a network of socio-affective brain regions including superior temporal sulcus (STS), orbitofrontal cortex, anterior cingulate cortex and fusiform face area (FFA). Of note, these patterns were observed in both the affected ASD group and the unaffected siblings and were specific to happy (but not fearful) faces, suggesting that neural anomalies in emotion processing may be potential neural endophenotypes of ASD. Using the same gender-identification task, acute tryptophan depletion (resulting in reduced

serotonin synthesis) was found to differentially affect neural activation depending on emotion type, such that those with ASD, following acute tryptophan depletion, showed generally decreased responses in socio-affective brain regions to emotional faces, except those expressing fear (Daly et al., 2012). Also in an incidental emotion processing task, ASD participants showed decreased amygdala habituation to both sad and neutral (but not fearful or happy) faces, and the diminished habituation was associated with increased autism symptom severity (Swartz, Wiggins, Carrasco, Lord, & Monk, 2013). Moreover, the ASD group showed reduced mPFC-amygdala connectivity while viewing sad faces, and this connectivity predicted amygdala habituation to sad faces in controls, suggesting that abnormal modulation of the amygdala by the mPFC may play a role in decreased habituation and the socio-affective impairments in ASD.

Medial PFC anomalies have also been reported in ASD participants performing emotion identification tasks and social decision-making tasks, suggesting neural impairments in self-related socio-affective processing. Specifically, when asked to identify emotions in pictures of themselves and others, individuals with ASD performed as well as non-psychiatric controls when identifying emotions in others, but show diminished ventral mPFC activation coupled with impaired behavioral accuracy particularly in the 'self' condition (Schulte-Ruther et al., 2011). Similarly, in a social decision-making task involving monetary exchange between human partners, high-functioning adolescents with ASD showed diminished dorsal cingulate cortex activity specifically during the 'self' decision-making phase, and the diminished neural responses varied parametrically with autism symptom severity (Chiu et al., 2008). In this study, similar to research employing the gender-identification task, the ASD group did not differ from matched controls in behavioral responses to signals of social partners. Together, these neuroimaging data suggest atypical self-awareness or self-related cognitive strategies in ASD that may contribute to

impaired insight into internal emotional states, a critical skill for optimal emotional functioning and socio-emotional regulation.

In an intriguing study that hints at behavioral strategies to target ER anomalies, Kliemann and colleagues (2012) directed participants with ASD to fixate on either the eyes or mouths of emotional faces. The fixation instruction was effective for both ASD and non-psychiatric control participants; however, the ASD participants were more likely to look away from the eyes following initial fixation and also showed relatively greater amygdala activation during eye fixation and decreased fixation during mouth fixation. These findings are consistent with those of Dalton and colleagues (2005), who found that amygdala activation to faces was modulated by gaze fixation in children with ASD but not in control children. The effects on amygdala activation of eye versus mouth fixation suggest that dysfunctional neural dynamics in ASD may involve substrates of both affective-avoidance and reduced orientation. Although this study did not use an explicit ER task, behavioral instructions were effective at directing initial affective attention, suggesting that behavioral strategies (e.g., disengagement, reallocation of attention) may lead to concomitant changes in neural activation that support improved ER.

Neural Substrates of Explicit ER and Cognitive Control in ASD

The studies summarized above indicate that ASD is characterized by anomalous patterns of brain activation in emotion-eliciting contexts. However, such paradigms do not directly address deficits in abilities to explicitly or consciously regulate emotional responses, processes that require cognitive control of emotional states. Two preliminary studies provide some insight into explicit ER impairments and their neural substrates in ASD. Pitskel and colleagues (2011) reported that typically developing children showed significant down-regulation of activation in the amygdala and insula when consciously and effortfully decreasing their affective responses to

gross pictures, while children with ASD did not exhibit similar down-regulation. In addition, Dichter and colleagues (2012) reported increased right dorsolateral prefrontal cortex activation in adults with ASD despite decreased modulation of the nucleus accumbens during explicit up-regulation of emotional responses to neutral social images, suggesting that individuals with ASD show evidence of compensatory activation in PFC during active ER, but that such compensatory activation does not result in typical modulation of emotion processing regions.

Outside of these two preliminary studies of cognitively effortful ER in ASD, there is a broad literature on impairments in cognitive control and associated neural activation in ASD. Functional MRI studies of cognitive control in ASD have revealed evidence of mostly hyperactivation (though in some contexts hypoactivation, likely due to task demands and analysis methods; Dichter, Felder, & Bodfish, 2009) in frontostriatal brain regions, including middle and inferior prefrontal cortex, anterior cingulate cortex (particularly in the dorsal region), as well as the basal ganglia. These studies used go/no-go, Stroop, and switching tasks (Schmitz, et al., 2006), all of which require interference inhibition (Dichter et al., 2009; Gomot, Belmonte, Bullmore, Bernard, & Baron-Cohen, 2008; Shafritz, Dichter, Baranek, & Belger, 2008; Solomon, et al., 2009), response monitoring (Thakkar, et al., 2008), novelty detection (Gilbert, Bird, Brindley, Frith, & Burgess, 2008; Just, Cherkassky, Keller, Kana, & Minshew, 2007), spatial attention (Gomot, et al., 2008), working memory (Allen, Muller, & Courchesne, 2004; Muller, Pierce, Ambrose, Allen, & Courchesne, 2001), and saccadic eye movements (Muller, Kleinhans, Kemmotsu, Pierce, & Courchesne, 2003). The broad pattern of prefrontal cortex hyperactivation in ASD in these studies is consistent with the ER findings of Dichter and colleagues (2012) and suggests that ASD may be characterized by compensatory PFC activation in contexts of cognitive control of both emotional and non-emotional information.

Neural Connectivity Among Socio-Affective Regions in ASD

The studies reviewed thus far are largely derived from task-based designs in which participants actively engage in ER-related cognitive processes (increase, decrease, or sustain emotions); however, studies that evaluate patterns of intrinsic brain connectivity have also revealed new insights into structural and functional alterations associated with ER impairments in ASD. Substantial data in non-clinical participants have shown that a key feature of neural responses to emotional information is modulation of cortico-limbic connectivity. Though there are no direct connections between lateral and dorsal PFC and the amygdala, there are indirect connections via mPFC (Maren & Quirk, 2004; Ongur & Price, 2000). Specifically, changes in emotional responses are associated with connectivity between PFC and limbic regions that has also been associated with self-reported affective reactions to both negative and positive stimuli (Heller et al., 2009; Johnstone et al., 2007; Urry et al., 2006).

Theoretical and empirical work has consistently underscored that ASD is likely characterized by a complex pattern of hyper- and hypo-connectivity (Di Martino et al., 2013; Just et al., 2012), and that developmental changes in the topology of connectivity may also play a role in the emergence and expression of core ASD symptoms (Washington et al., 2014). While no studies have explicitly targeted the connective properties of ER-related regions in the context of ASD, the results of several large scale studies of whole-brain intrinsic connectivity provide some context for understanding how ER networks might be disrupted.

The largest connectivity study to date was reported by Di Martino and colleagues (2013) and focused on resting-state analyses of ASD data from the Autism Brain Imaging Data Exchange (ABIDE) consortium. Whole-brain estimates of intrinsic connectivity and related graph-theoretic parameters revealed evidence of hypo-connectivity of mid- and posterior insula

and posterior cingulate cortex, a finding highly consistent with related studies in ASD that report anomalous connective and task-based properties of emotion-relevant regions of the brain including the insula (Ebisch et al., 2011; Di Martino et al., 2009; Uddin & Menon, 2009). The insula is thought to play a role in task-related information processing and monitoring of interoceptive information (Cloutman et al., 2012; Kurth et al., 2010; Mutschler et al., 2009), particularly for the purposes of merging information about visceral experience with affective context (Dolan, 2002; Phillips, Drevets, Rauch, & Lane, 2003). The insula may also play a role in coordinating the competitive interactions between task-positive (i.e., executive control; salience) networks and task-negative (i.e., default-mode) networks (Uddin & Menon, 2009), that collectively modulate task performance across behavioral tasks with varying sensory, affective and response demands. Dysfunction in the connective properties of the insula would likely impact the excitation-inhibition balance of this region, leading to failures in the coordination of task-based and resting-state networks and poorer integration of information across sensory modalities and emotional interoception and empathetic or perspective-taking processes (although, see Bird and colleagues [2010]). Of interest, alterations in the functionality and connective properties of the insula are also closely associated with anxiety traits (Baur, Hänggi, Langer, & Jäncke, 2013; Klumpp Angstadt & Phan, 2012; Paulus & Stein, 2006; Stein, Simmons, Feinstein, & Paulus, 2007), which may provide some initial clues into to the functional overlap between ASD and anxiety.

In addition to alterations in the connective properties of brain areas implicated in the generation and experience of emotions, there is evidence of ASD-specific alterations in connectivity of other brain regions involved in social cognition. Bachevaliera and Loveland (2006) have proposed that dysregulated frontostriatal-temporal connectivity mediates social

deficits in ASD, that damage to these structures results in poor social decision making (Bechara, Damasio, Damasio, & Lee, 1999), and that structural and functional brain imaging studies have corroborated temporal and frontal lobe abnormalities in ASD (Dichter, 2012). More recently, resting state functional connectivity among fronto-limbic-social regions has been shown to be markedly reduced in ASD, and the reduction is associated with increased communication deficits and predictive of poor emotion recognition performance, respectively (Abrams et al., 2013; Alaerts et al., 2013). These studies point to disrupted neural connectivity in ASD and highlight that alterations in connectivity among brain regions associated with cognitive, emotional or social function may contribute to a broad collection of deficits in social cognition that subserve ensuing socio-affective dysfunction in ASD (Just et al., 2007; Kana, Keller, Minshew, & Just, 2007; Kennedy & Courchesne, 2008).

Summary

Neuroimaging studies have advanced our understanding of the wider networks of interactive and overlapping brain regions that broadly support ER. Although studies directly examining ER in ASD remain sparse, the extant findings provide an emerging picture of neural anomalies associated with emotion processing in ASD that may mediate or moderate downstream ER impairments. Specifically, the rich literature on brain correlates of social-affective processing in ASD implicates deficits in overlapping circuitry, including the mPFC, amygdala, cingulate cortex, and orbitofrontal cortex (though see Vander Wyk, Hoffman, & Pelphrey (2013) for data suggesting neural activation differences may be driven by task demands). Of importance, these brain regions are those implicated in ER and have been identified as disrupted in explicit and implicit ER deficits across anxiety disorders (Ball, Ramsawh, Campbell-Sills, Paulus, & Stein, 2013; Blair et al., 2012; Etkin, Prater, Hoeft, Menon,

& Schatzberg, 2010; Etkin & Schatzberg, 2011; Goldin, Manber, Hakimi, Canli, & Gross, 2009; Goldin, Manber-Ball, Werner, Heimberg, & Gross, 2009). Although the precise interactions among aberrant neural substrates of emotion processing, ASD, anxiety, and ER remain unknown, these findings emphasize that aberrant emotional processing in ASD and anxiety may arise through (or be due to) common anomalies in neural engagement and connectivity associated with socio-affective or cognitive processing.

Disrupted ER as Anxiety in People with ASD

In this section, we explore factors that may moderate the expression of impaired ER, making it more likely that ER difficulties are expressed as anxiety. Though clearly anxiety is not the only possible manifestation of impaired ER, and not everyone with ASD presents with significant anxiety symptoms, it remains a commonly presented clinical problem in ASD. The moderating factors discussed below are those with the strongest research base, but in no way capture *all* of the processes that may contribute to ER deficits manifesting as anxiety.

Cognitive Factors

Cognitive factors, such as biases in perception and interpretation, may contribute to the experience of anxiety in people with ASD. Cognitive bias to perceived threat is commonly considered an etiological factor in the development of anxiety disorders. Anxious children and adults tend to focus attention, overtly and covertly, on potential indicators of threat or danger (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007). Biased attention and information processing is apparent in orienting, perception, and interpretation. For instance, anxious people tend to show attentional bias (orienting) toward threatening faces (e.g., Weissman, Chu, Reddy, & Mohlman, 2012), perceive neutral faces as threatening (Yoon & Zinbarg, 2008), and interpret ambiguous or novel stimuli negatively (Pine, Helfinstein, Bar-

Haim, Nelson, & Fox, 2009). Attention, essentially, is the gatekeeper in determining what information we perceive and process.

In ASD, decreased visual attending to social cues is largely assumed to stem from lack of appreciation for the social relevance of eye gaze (e.g., Klin, Jones, Schultz, & Volkmar, 2003), such that social stimuli (e.g., human faces) are not as meaningful as they are for typically developing people (Dawson et al., 2008). Eye-tracking research has generally supported this view, finding that adolescents (Fletcher-Watson, Leekam, Benson, Frank, & Findlay, 2009; Klin et al., 2002) and adults (Pelphrey et al., 2002) with ASD visually attend less to social stimuli than do peers without ASD. However, research assessing gaze patterns, neural circuitry, and autonomic arousal (e.g., Dalton et al., 2005; Joseph et al., 2008) has indicated that, for some people with ASD, perhaps aversion and heightened emotional reactivity, both of which are core components of social anxiety, may contribute to the observed lack of attending to others' eye gaze and facial features.

As such, altered alerting and attention to social and non-social stimuli may predict (or reflect) anxiety. Decreased attending to social stimuli may, for at least some people with ASD, stem from active avoidance or aversion, rather than decreased salience of the stimuli. It is also possible that under-attending to social stimuli reflects over-orienting to non-social sources of potential threat in the environment, or lack of automatic social referencing for support or comfort when distressed. There is also preliminary evidence for a possible interpretation bias in ASD. Kuusikko and colleagues (2009) found that youth with ASD were more likely than peers without ASD to perceive ambiguous faces as portraying negative emotions, suggesting biased interpretations. Eack et al (2013) similarly found that adults with ASD perceived neutral faces as negative whereas typically developing adults did not. In summary, in the presence of atypical

visual attending to the environment - specifically aversion to social stimuli and bias toward threat cues, ER impairments may be expressed as anxiety.

Social Factors

The social impairment that is the primary defining feature of ASD may both directly (e.g., via social confusion) and indirectly (e.g., via negative feedback from others) contribute to the manifestation of ER deficits as anxiety. Higher functioning individuals with ASD are often aware of their inability to master social demands, though many such individuals place as much emphasis on the importance of peer approval as typically developing peers (Williamson, Craig, & Slinger, 2008), and many individuals with ASD are sensitive to social feedback. This awareness is hypothesized to contribute to the development of secondary social anxiety and heightened fear of negative peer evaluation (White & Roberson-Nay, 2009). Awareness of one's social impairments may interact with poor ER to produce anxiety, contributing to anxious rumination and distorted interpretation of others' intentions and responses.

In addition, it has been proposed that core features of ASD (e.g., odd social behaviors) may in fact contribute to the development of anxiety, especially during adolescence (White et al., 2013). Behaviors that are developmentally inappropriate for the social context (e.g., intruding into a conversation, saying something inappropriate in class, revealing one's belief in mythical entities or superheroes during adolescence) often result in negative feedback from peers and become quite humiliating for the person with ASD. Such experiences, in the context of an inability to cope effectively with these feelings and alter one's behavior accordingly, could contribute to various forms (e.g., separation, social) of anxiety.

Some individuals with ASD seek social interaction and experience excessive arousal in relation to social stimuli (Kleinhans et al., 2010; White, Bray, & Ollendick, 2012; White et al.,

2010). Sensitivity to social cues, in particular faces, may moderate expression of ER deficits as anxiety. People with ASD who have greater amygdala activation during social information processing tasks report more difficulty with social anxiety (Kleinhans et al., 2010). Motivation for interactions, in the context of awareness of critical feedback and one's own social deficits, could engender anxiety, especially anxiety related to fear of negative evaluation, which is a hallmark of social anxiety disorder (APA, 2013). The extant research on social motivation and anxiety in ASD has not consistently found evidence for social motivation in ASD, however. In a study examining brain responses to directed versus averted gaze in emotional faces, Davies and colleagues (2011) showed strong differentiation in VLPFC between directed and averted gaze in controls, but no such differentiation in participants with ASD. The authors suggested that this pattern indicates generally reduced social motivation in ASD, rather than anxiety, as eye gaze cues are thought to contribute to socio-affective interpretation and regulation.

Individuals prone to neuroticism are more likely to develop clinical anxiety problems, rather than a non-anxiety disorder, when the environment is chronically threatening (LeDoux, 2000). It is possible that people with ASD, including those without cognitive impairments, struggle to navigate a social world that is devoid of clear directions or rules, and in which change is nearly constant. Interpersonal communication may be a threatening and stressful situation for most people on the spectrum. Adolescents with ASD show greater bilateral activation in neural substrates involved in processing socio-emotional stimuli, specifically the amygdala, vPFC, and striatum, relative to peers without ASD (Weng et al., 2011). This pattern suggests increased ambiguity in interpretation of facial cues and distress owing to viewing others' facial expressions. Processing faces may require more effort in people with ASD, which may be attributable to less experience with faces over the course of childhood (less cumulative

experience, owing to not attending to facial stimuli; e.g., Osterling & Dawson, 1994) and impaired ability to interpret others' facial emotions (Weng et al., 2011). Tupak and colleagues (2014) speculated that anxiety may reflect a lowered threshold for PFC activation, owing to greater, nearly chronic, demand for regulation of heightened negative affect, even during non-threatening tasks. Deficits in recognition and expression of emotions in self and others, limited social experience, and a near-constant sense of ambiguity may contribute to chronic confusion about social world, which could give rise to anxiety.

Behavioral Factors

ER impairments also likely contribute to anxiety via conditioning and avoidance. Inability to tolerate distress or fear and cope with these feelings contributes to conditioned fear responses. Avoidance perpetuates anxiety, as reduction in experienced anxiety reinforces avoidance behavior. Longitudinal research (McLaughlin et al., 2011) supports this directionality, such that ER deficits predict psychopathology such as anxiety. In addition to avoidance and escape being behavioral indicators of the presence of anxiety (Ozsivadjian, Knott, & Magiati, 2012). Avoidance (as a maladaptive ER strategy) may also contribute to, or worsen, anxiety in people with ASD. For example, a 10-year-old girl with ASD may experience dread related to possible changes in her school schedule (a symptom of ASD). She may struggle to manage the distress and seek constant reassurance from parents and teachers (poor ER). The distress contributes to her avoidance of school, and she refuses to work at school (avoidance behaviors). As a result, she may never develop strategies to cope with schedule changes or to manage the associated negative affect and her anxious avoiding behaviors are strengthened.

Sensory issues have long been suggested as a possible determinant of anxiety in individuals with ASD, and sensory symptoms correlate with anxiety severity in children with

ASD (Ben-Sasson et al., 2008), although the potential causal linkages and direction of effects between anxiety and sensory over-responsivity in ASD have not yet been fully determined (Green & Ben-Sasson, 2010). One possible mechanistic account of the relation between anxiety and sensory over-responsiveness in ASD is that anxious individuals with ASD may exhibit hyper-vigilance regarding the sensory environment that causes impairments in shifting attention and decreasing accompanying negative affectivity (Craske, 2003), though, as reviewed earlier, clearly not all individuals with ASD exhibit general hyper-arousal (Rogers & Ozonoff, 2005). Alternatively, it may be the case that sensory over-responsiveness and anxiety in ASD are linked via a third common causal factor, such as functional amygdala abnormalities given the role the amygdala plays in integration of sensory input with response to perceived threat (Zald, 2003). Whereas the neural substrates of anxiety in ASD have not yet been fully examined, a recent study testing sensory over-responsivity in ASD provides initial evidence that sensory issues are related to anxiety. In this study, in response to aversive auditory stimuli, participants with ASD, relative to controls, displayed greater activation in primary sensory cortical areas, as well as in the amygdala and orbital-frontal cortex, regions implicated in ER (Green et al., 2013). Of note, activation in these areas was correlated with ratings of both anxiety and sensory over-responsivity.

Conclusions

In this review, we have presented a model that considers causal pathways to ER impairments in ASD and factors that moderate these impairments to result in anxiety. We have framed our examination of ER deficits and anxiety in ASD from a developmental psychopathology lens, within the complementary processes of equifinality and multifinality (cf. Cicchetti & Rogosch, 1996). We propose that impaired ER may be the result of a number of

disease pathways (i.e., equifinality). Impaired ER, in turn, can be manifested in a multitude of ways (i.e., multifinality), including anxiety. The clinical expression of ER impairment is affected by cognitive, social, and behavioral factors. In Figure 1, we propose a developmental model of ER impairment and anxiety in ASD, that is adapted from Nolen-Hoeksema and Watkins' (2011) heuristic model for understanding how transdiagnostic processes can help explain multifinality in developmental psychopathology.

<Figure 1>

The primary limitation of this review is that the proposed model is largely, as yet, untested and draws fairly heavily from research with other forms of psychopathology, due to the limited body of research on ER functioning in ASD. This is perhaps most apparent in the dearth of studies that have directly examined relationships between ER and anxiety in people with ASD. Owing to the limited research base from which to draw, it is difficult to draw firm conclusions and we have proposed a model which is yet to be tested empirically. Clearly, more research is needed in this area. Longitudinal research, including studies of the effects of treatments specifically targeting ER impairments, will be needed to examine the causal effects of ER on the emergence of anxiety symptoms in children with ASD. Consideration of possible ER impairments should also inform treatment research. Specifically, establishing temporal precedence of change in ER function prior to change in the targeted behavioral outcomes (e.g., anxiety, depression) during intervention could inform our understanding of mechanisms of change. This focus on linking the hypothesized mechanism of change with manifest clinical effects is consistent with federal funding changes related to the structure of clinical trials.

Consistent with the model proposed by Mazefsky and colleagues (2013), we conceptualize deficits in ER as being intrinsic to ASD, such that ASD itself affects mechanisms

that give rise to ER impairments. This conceptualization differs from how ER impairments are typically considered in other forms of psychopathology, in which ER problems presage and/or cause the expressed pathology (McLaughlin et al., 2011). We have applied the heuristic proposed by Nolen-Hoeksema and Watkins (2011) to examine neural, physiologic, and socio-cognitive *distal* risk processes, which mediate the experience of deficiencies in ER. ER impairments are conceptualized as an intermediate, or *proximal*, transdiagnostic risk factor, which can be manifested in a number of ways such as aggression, intense irritability, self-harm, or anxiety. In the final analysis, moderators of this proximal risk factor determine what specific symptoms are experienced.

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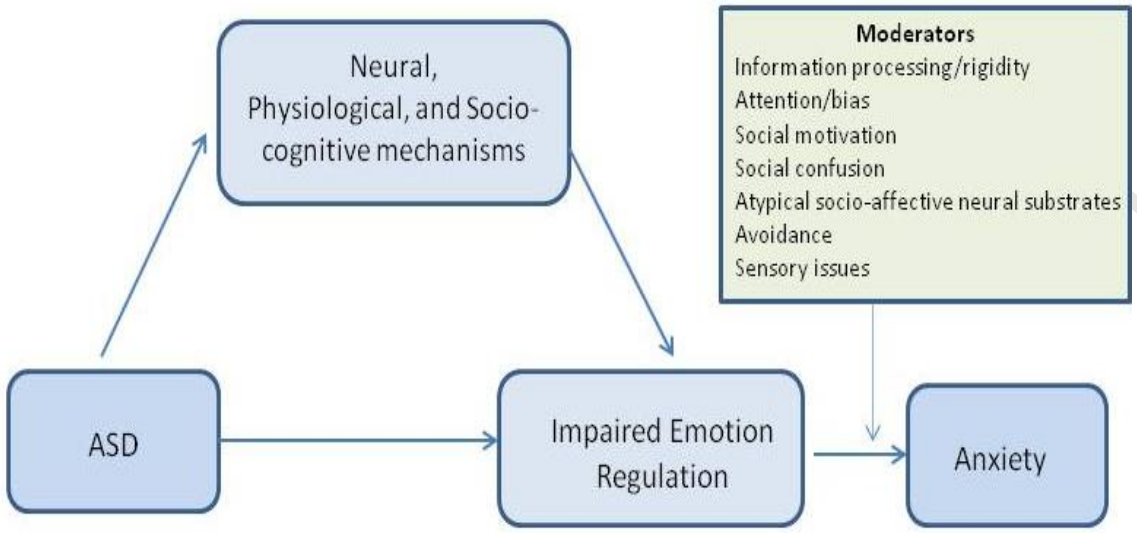

Figure 1

Mediators of ER Deficits in ASD and Moderators of Anxiety Expression

Social-cognitive, physiological, and neural mechanisms underlying emotion regulation impairments: Understanding anxiety in autism spectrum disorder

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