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S.I. : EMPATHY IN AUTISM

Empathy in Autism Spectrum Disorder

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Abstract
Empathy is an essential component of human social life. It requires the ability to understand another's mental state and respond with an appropriate emotion or action. Individuals with autism spectrum disorder (ASD) have been described to exhibit atypical empathic responses which limit communication and social interactions. This review highlights the clinical characteristics and mechanisms underlying empathy in ASD by summarizing 61 peer-reviewed articles. Studies characterized empathic differences due to sex, age, intelligence, and disorder severity and provided valuable insights into the roles that genetics, neural networks, and sensory processing have in eliciting empathy. This knowledge will lead to improved diagnostics and therapies to improve social cognition, emotional recognition, and the empathic response in patients with ASD.

Keywords Empathy · Autism spectrum disorder · Autism · Asperger syndrome · Autistic traits

Introduction

Autism Spectrum Disorder

Autism spectrum disorder (ASD) consists of a range of neurodevelopmental disorders in which individuals show deficits in social communication and social interaction along with repetitive behavior and restricted interests (American Psychiatric Association 2013). First described in the 1930s, autism represents the primary disorder within ASD. Autism has two subtypes: high-functioning autism (HFA) and low-functioning autism (LFA). Individuals with HFA have a typical IQ and relatively mild symptoms as compared to individuals with LFA. Once a separate diagnosis, Asperger syndrome (AS) became part of ASD in 2013, as formalized in the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5). Individuals with AS have typical to strong verbal skills and intellectual ability, which distinguishes AS from other forms of autism. Autism symptoms also typically present in early childhood and include delays in language (Kanner 1943), whereas AS is usually diagnosed at a later age and without language delays. However, more recent findings have shown that non-verbal language delays appear in children who are later diagnosed with AS (Cederlund and Gillberg 2004; Gillberg and Cederlund 2005).

Current estimates of the prevalence of ASD suggest 1 in 68 children are diagnosed (U. S. Department of Health and Human Services 2014). In the early 1970s, the prevalence of diagnosed autism was only 1 in 2500 (McDonald and Paul 2010). It remains unclear whether this change is attributed to a true increase in the condition or due to broadened diagnostic criteria, better diagnostic procedures, and improved awareness of potentially affected children within our society (Hertz-Picciotto and Delwiche 2009). It has been suggested that environmental factors may play a role in the unexplained change in ASD prevalence (Landrigan et al. 2012). Several prenatal and perinatal complications have been reported as possible risk factors for ASD. These risks include prenatal chemical exposures (e.g., thalidomide, valproic acid, methylmercury from fish consumption), perinatal oxygen insufficiency, premature birth, and advanced maternal and paternal age (Arndt et al. 2005; Gardener et al. 2011; Hultman et al. 2011; Parner et al. 2012; van Wijngaarden et al. 2013). An important area of ASD research will involve studying how environmental factors and genetic susceptibilities interact.

Although ASD is considered a universal disorder and these rates are consistent across cultures (Mash and Barkley 2003), there is a predominant male bias. The average male-to-female ratio for ASD is approximately 4:1 (Fombonne 2009). This bias may be attributed to females being

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underdiagnosed since they exhibit fewer atypical behaviors common to ASD (Tsakanikos et al. 2011). ASD has been conceptualized as an extreme of the typical male brain; individuals with ASD prefer systemizing (male-dominant trait) over empathizing (female-dominant trait) (Baron-Cohen 2002). Systemizing involves developing rules and arranging things according to a system. Empathizing is the ability to understand and share the feelings of another by attributing mental states to others. Accordingly, people with ASD have difficulties with empathy, which is likely related to social communication deficits in mindreading and emotional recognition (Frith 2001; Schulte-Rüther et al. 2011).

Alternative theories to the extreme male brain theory of ASD include deficits in Theory of Mind (ToM), simulation theory, and the social motivation hypothesis. ToM is the ability to recognize that other people's mental states (i.e., beliefs, intents, desires, emotions, knowledge) may differ from one's own (Premack and Woodruff 1978). A well-developed ToM helps us solve conflicts, develop social skills, and predict other peoples' behavior (Gweon and Saxe 2013). Since many individuals with ASD have difficulty assigning mental states to others, it has been suggested that they lack ToM capabilities (Baron-Cohen et al. 1985; Korkmaz 2011). In contrast, simulation theory posits that inferences about others' mental states arise by imaginatively projecting oneself into the place of another person and simulating what they might believe, desire, or intend (Currie 1996). These "mindreading" capabilities are thought to arise from using special mirror neurons which fire when observing an action performed by another (Gallese and Goldman 1998; Iacoboni et al. 2005). In ASD, reduced empathic responses may be attributed to mirror neuron dysfunction, better known as the broken mirror hypothesis (Dapretto et al. 2006). The social motivation hypothesis proposes that social stimuli are less rewarding to individuals with ASD due to underlying neural abnormalities in reward processing (Cox et al. 2015; Delmonte et al. 2012; Scott-Van Zeeland et al. 2010).

Affective Versus Cognitive Empathy

The word "empathy" has only been around for the last century and originates from the German word *Einfühlung*, which means "feeling into" (Gallese 2003; Titchener 2014). As its translation suggests, empathy involves feeling our way into the lives of others through an instinctive mirroring of others' experience (Keen 2006). Undoubtedly, human empathy is an essential component of our society. Empathy is a motivating factor for unselfish, prosocial behavior that allows people to create connections, develop bonds of trust, and gain insights into the actions of others (Eisenberg and Miller 1987).

The complex nature of empathy requires an individual to understand another's mental state and to respond with an appropriate emotion or action. Empathy has two major components: (1) cognitive empathy, which denotes the ability to understand another person's perspective; and, (2) affective (or emotional) empathy, which is the observer's emotional response to the mental state of others (Cox et al. 2012; Rogers et al. 2007; Shamay-Tsoory et al. 2009b). Although defined separately, these two approaches to empathy are related. Studying them together helps increase our understanding of empathy (Davis 1980, 1983).

Atypical empathic responses have often been associated with ASD (Baron-Cohen and Wheelwright 2004; Blacher et al. 2003; Gillberg 1992; Shamay-Tsoory et al. 2002) as well as other psychiatric illnesses. Cognitive empathy is impaired in ASD, bipolar disorder, and borderline personality disorder (Deschamps et al. 2014; Dziobek et al. 2008; Harari et al. 2010; Mazza et al. 2014; Moriwaki et al. 2011; Rueda et al. 2015; Shamay-Tsoory et al. 2009a). Affective empathy is impaired in psychopathy, schizophrenia, depersonalization, and narcissism (Blair 2005; Jones et al. 2010; Lawrence et al. 2007; Ritter et al. 2011; Shamay-Tsoory et al. 2007). Even among neurotypical individuals, a normal variation between affective and cognitive components accounts for the differences in empathic experiences.

Given the importance of empathy in human social functioning and the increase in the prevalence of autism spectrum disorders, a critical review focusing specifically on empathy in ASD is warranted. Currently, there is no cure for autism, and although existing treatments are effective in improving quality of life and functional independence, few therapies focus on improving emotion regulation in social situations. While previous reviews have addressed emotional impairments in ASD, the focus has been on understanding emotion-processing (Nuske et al. 2013) and Theory of Mind (Peterson 2014)—concepts which are both necessary for the empathic response—but do not fully explain the complex process of empathy. Consolidating our current knowledge about empathy in ASD is important. It will equip clinical and research practices to improve diagnostics and therapies. This consolidation can be achieved by critically examining empathy in the context of clinical characteristics of individuals with ASD and the mechanisms that cause empathic deficits.

Methods

This critical review uses peer-reviewed literature on empathy and ASD obtained from publicly accessible literature databases: PubMed, PsycINFO, and Embase. These databases were used to extract clinically relevant research on clinical characteristics of individuals with

ASD, mechanisms that cause empathic deficits in ASD, and emerging diagnostics and therapies. While theoretical and conceptual contributions were equally likely to be identified using these databases, relevant articles from related areas (e.g., sociology, cultural anthropology) were less likely to be identified. Given the breadth of research in the field, article titles were searched using only the following search string: "empathy" AND ("autism" OR "Asperger" OR "autism spectrum disorder"), resulting in 233 reports (i.e., PubMed: 70, PsycINFO: 86, Embase: 77). After the removal of duplicates, 117 reports remained. Titles and abstracts were screened to select human studies that were original, peer-reviewed, and written in English. Relevant studies identified through other sources were also assessed for eligibility. Figure 1 provides an overview of the selection process which led to the inclusion of 61 relevant articles.

Results

Research on empathy in ASD began in the early 2000s and has increased in popularity within the scientific ASD community over the last one and a half decades (Fig. 2). Within the literature, 61 publications focused specifically on empathy in ASD (Table 1). For this review these papers have been categorized by their subject population: 16 studies on generalized ASD (i.e., LFA, HFA, AS), 31 studies on high-functioning ASD (i.e., HFA, AS), eight studies on only AS, and six studies on autistic traits (Fig. 3a).

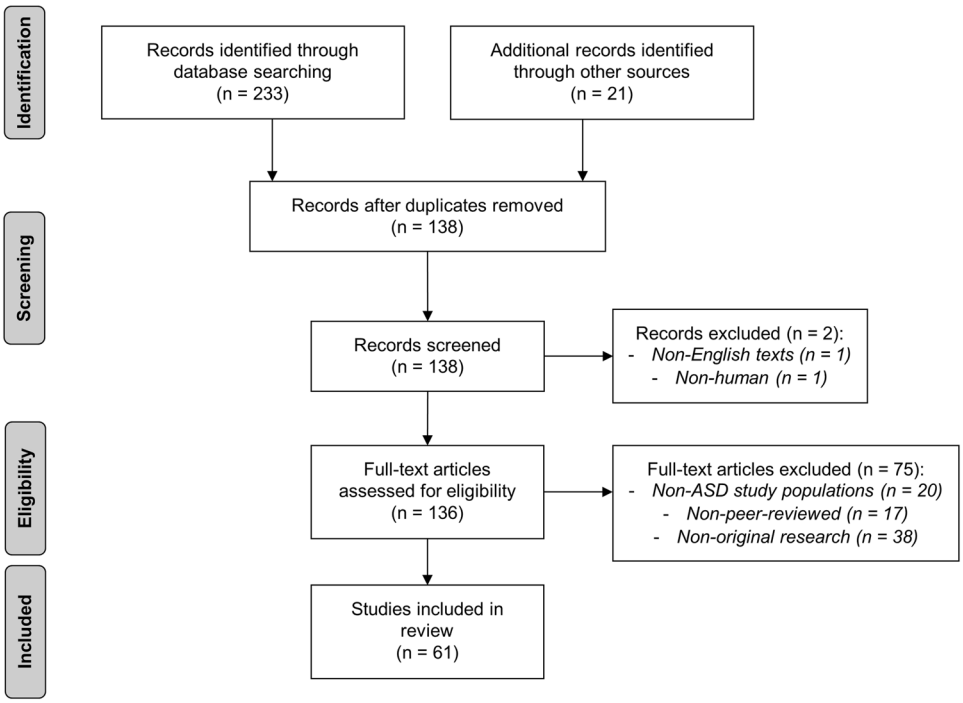

Fig. 1 Flowchart indicating the number of records that were identified, screened, eligible, and included in the review

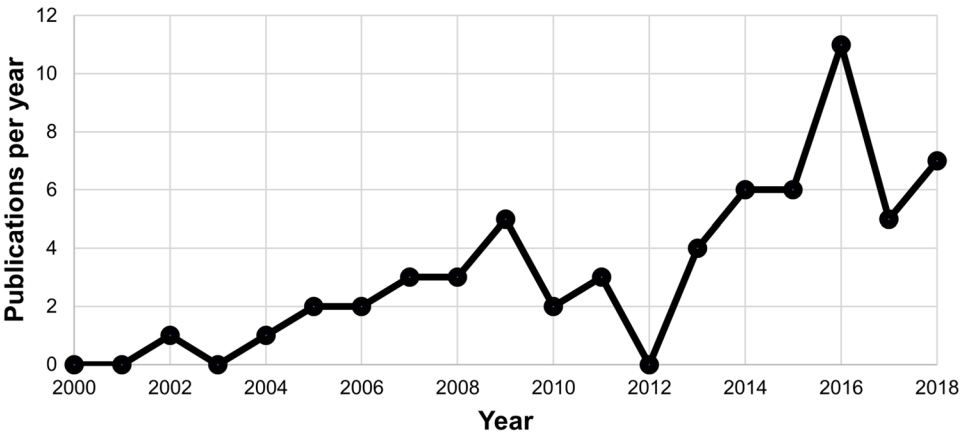

Fig. 2 Yearly growth in the number of publications on empathy in ASD from 2000 to 2018. Over the last one and a half decades, 61 original research papers on empathy in ASD were published

Table 1 Studies examining empathy in individuals with autism spectrum disorder

No.	Study	Disorder subtype	Theme
1	Althaus et al. (2015)	HF-ASD	Therapy
2	Auyeung et al. (2009)	ASD	Sex effect
3	Baron-Cohen et al. (2005)	ASD	Sex effect
4	Baron-Cohen et al. (2014)	ASD	Sex effect
5	Baron-Cohen et al. (2015)	HF-ASD	Sex effect
6	Baron-Cohen and Wheelwright (2004)	HF-ASD	Diagnostic tool
7	Bellebaum et al. (2014)	HF-ASD	Mechanism
8	Cascia and Barr (2017)	ASD	Disorder severity
9	Chakrabarti et al. (2009)	Asperger syndrome	Mechanism
10	Chen et al. (2017)	HF-ASD	Mechanism
11	Clark et al. (2008)	HF-ASD	Mechanism
12	Colombi and Ghaziuddin (2017)	ASD	Disorder severity
13	De Coster et al. (2017)	HF-ASD	Mechanism
14	Deschamps et al. (2014)	HF-ASD	Empathy component
15	Dziobek et al. (2008)	Asperger syndrome	Diagnostic tool
16	Eyuboglu et al. (2017)	Autistic trait	Disorder severity
17	Gökçen et al. (2016)	Autistic trait	Age effect
18	Golan and Baron-Cohen (2006)	HF-ASD	Therapy
19	Goldenfeld et al. (2005)	ASD	Sex effect
20	Greimel et al. (2010)	HF-ASD	Mechanism
21	Grove et al. (2014)	Autistic trait	Disorder severity
22	Gu et al. (2015)	HF-ASD	Mechanism
23	Hoffmann et al. (2016)	HF-ASD	Mechanism
24	Holopainen et al. (2018)	HF-ASD	Therapy
25	Jones et al. (2010)	ASD	Empathy component
26	Klapwijk et al. (2016)	ASD	Mechanism
27	Koegel et al. (2016)	ASD	Therapy
28	Koehne et al. (2016a)	HF-ASD	Therapy
29	Koehne et al. (2016b)	HF-ASD	Mechanism
30	Lai et al. (2011)	HF-ASD	Sex effect
31	Larson et al. (2015)	ASD	Disorder severity
32	Lassalle et al. (2018)	HF-ASD	Mechanism
33	Lepage et al. (2009)	ASD	Diagnostic tool
34	Lombardo et al. (2007)	HF-ASD	Mechanism
35	Malcolm et al. (2017)	ASD	Therapy
36	Mathersul et al. (2013)	HF-ASD	Diagnostic tool
37	Mazza et al. (2014)	ASD	Empathy component
38	McDonald et al. (2016)	Autistic trait	Mechanism
39	Minio-Paluello et al. (2009)	Asperger syndrome	Mechanism
40	Montgomery et al. (2016)	HF-ASD	Disorder severity
41	Moriwaki et al. (2011)	HF-ASD	Empathy component
42	Mul et al. (2018)	HF-ASD	Mechanism
43	Preckel et al. (2016)	ASD	Therapy
44	Rigby et al. (2018)	HF-ASD	Mechanism
45	Robinson and Elliott (2016)	Asperger syndrome	Diagnostic tool
46	Rogers et al. (2007)	Asperger syndrome	Empathy component
47	Roine et al. (2015)	Asperger syndrome	Mechanism
48	Rueda et al. (2015)	Asperger syndrome	Empathy component
49	Scheeren et al. (2013)	HF-ASD	Age effect
50	Schrandt et al. (2009)	ASD	Therapy
51	Schulte-Rüther et al. (2011)	HF-ASD	Mechanism

Table 1 (continued)

No.	Study	Disorder subtype	Theme
52	Schulte-Rüther et al. (2014)	HF-ASD	Age effect
53	Schulte-Rüther et al. (2017)	HF-ASD	Mechanism
54	Shamay-Tsoory et al. (2002)	Asperger syndrome	Empathy component
55	Silani et al. (2008)	HF-ASD	Mechanism
56	Sucksmith et al. (2013)	ASD	Disorder severity
57	Truzzi et al. (2016)	Autistic trait	Diagnostic tool
58	Wakabayashi et al. (2007)	HF-ASD	Sex effect
59	Warrier et al. (2013)	Asperger syndrome	Mechanism
60	Wheelwright et al. (2006)	HF-ASD	Sex effect
61	Yoshimura et al. (2018)	HF-ASD	Diagnostic tool

HF-ASD high-functioning autism spectrum disorder, *ASD* autism spectrum disorder

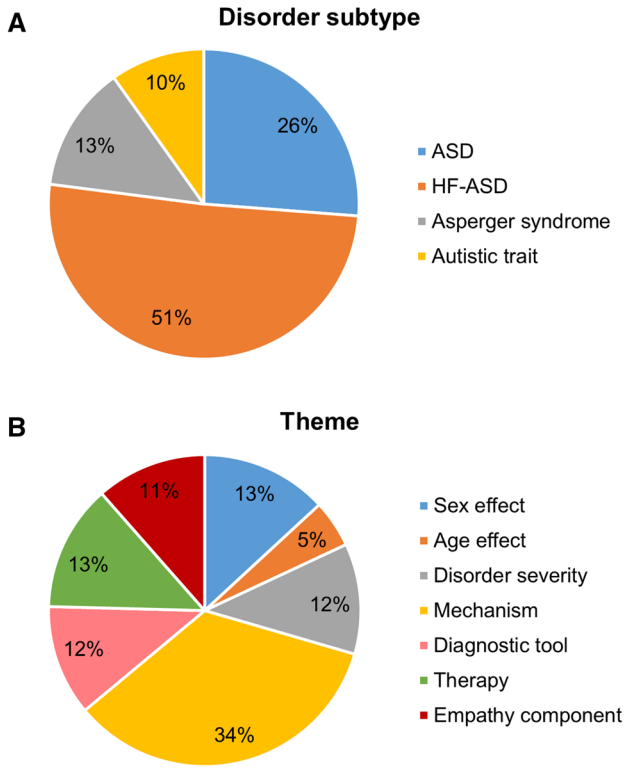

Fig. 3 Categorization of the reviewed literature by research subject populations and recurring themes. **a** Classification by disorder subtype: ASD includes LFA, HFA, and AS; HF-ASD includes HFA and AS. **b** Classification by theme. *ASD* autism spectrum disorder, *HF-ASD* high-functioning autism spectrum disorder, *LFA* low-functioning autism, *HFA* high-functioning autism, *AS* Asperger syndrome

Another categorization was based on recurring themes. Eighteen studies characterized empathic differences based on sex, age, and disorder severity (eight, three, and seven papers respectively). Twenty-one studies characterized possible mechanisms that cause empathic deficits in ASD. Fifteen studies characterized new diagnostic tools and therapies (seven and eight papers respectively). Lastly, seven studies compared cognitive components versus affective components of empathy in ASD (Fig. 3b).

Characterizing the Empathic Response in ASD

Sex-Related Differences in Empathy

Sex is a risk factor for ASD; males are four times more likely to be diagnosed than females (Fombonne 2009). Since males typically exhibit more systemizing over empathizing traits (opposite for females) (Goldenfeld et al. 2005), the extreme male brain theory suggests that autism represents an exaggerated male profile (impaired empathizing and enhanced systemizing).

Interestingly, neuroanatomical studies have shown that brains of individuals with ASD represent extremes of the typical male brain (Baron-Cohen et al. 2005). The size of brain regions in individuals with autism are below-average for the anterior cingulate, superior temporal gyrus, prefrontal cortex, and thalamus (structures that are normally smaller in males than females), and above-average for the amygdala and cerebellum (structures that are normally larger in males than females). Measures of head circumference and weight of the brain in people with autism are also above-average, which aligns with the fact that typical male brains are larger than female brains. Other research groups replicated some of these neuroanatomical findings, including a longitudinal volumetric MRI study by Barnea-Goraly et al. (2014) which concluded that children with ASD tend to have a larger amygdala.

In a study by Baron-Cohen et al. (2015) which measured cognitive empathy through an advanced test of ToM, typical sex differences were absent among adults with ASD, providing support for the extreme male brain theory. Similarly, studies that analyzed systemizing-empathizing profiles of children and adults with ASD reported that both groups tend towards a hyper-masculinized profile, irrespective of sex (Auyeung et al. 2009; Lai et al. 2011; Wakabayashi

et al. 2007; Wheelwright et al. 2006). However, behavioral sex differences did emerge (e.g., sensory symptoms, socio-communication deficits) which may reflect different developmental mechanisms between males and females with ASD (Lai et al. 2011). Females were shown to have improved socio-communication skills which mask symptom severity and may explain the underdiagnosis of females with ASD.

In a larger study (over 800 participants with ASD), typical sex differences for empathy were attenuated but not completely absent in adults with autism (Fig. 4) (Baron-Cohen et al. 2014). While a shift to the extreme of the male profile was observed in both males and females with ASD, the persistence of normative sex differences might necessitate separate thresholds based on sex for the clinical diagnosis of ASD. It has been hypothesized that a selection bias may exaggerate hypermasculinization of women on the autism spectrum. Current diagnostic criteria for ASD fail to integrate sex-specific characteristics and focus predominantly on male-specific behavior (Kok et al. 2016).

Age- and IQ-Related Differences in Empathy

Early theorists believed that young children were not able to experience empathy because they were too egocentric or lacked the cognitive ability (Freud 1958; Piaget 1965). However, numerous studies have shown that very young children can display empathic behaviors, despite challenges related to their limited verbal expressiveness (Zahn-Waxler et al. 1979, 1992a, b). Developing empathy is a gradual process that begins with reflexive crying in newborns, empathic responding and helping behavior in toddlers, advances in cognitive empathy in early childhood, and the stability of empathy as a trait into adulthood (McDonald and Messinger 2010).

Since deficits in empathy have been observed in preschoolers with ASD (Begeer et al. 2008; Yirmiya et al. 1998), Scheeren et al. (2013) studied the effects of age and intelligence on empathic responsiveness by comparing children and adolescents with ASD. Results suggest that above a particular threshold, IQ may not significantly add to differences in empathic responsiveness. Instead, age may better explain empathy deficits in younger children with ASD. In a separate study focusing on autistic traits in typically developing adults and adolescents, findings showed that mentalizing ability and executive control needed for empathic processing improved with age (Gökçen et al. 2016). Age-dependent changes have also been observed in the neural substrates of empathy in ASD (Schulte-Rüther et al. 2014). Functional magnetic resonance imaging (fMRI) revealed that increased age-related activation of the right prefrontal, right parietal, and occipital cortices might indicate the development of compensatory mechanisms in individuals with ASD. Early intervention is imperative to promote the development of these mechanisms that improve empathy.

Disorder Severity and Degree of Empathy

Disorder severity is related to intellectual ability. IQ determines whether an individual with autism is low-versus high-functioning. Evidence suggests that increased vocabulary and executive function skills are associated with higher empathy scores (Cascia and Barr 2017). Even among groups with similar empathy and IQ scores, AS individuals perform better than people with HFA on clinical tests that require advanced mentalizing and complex emotion recognition (Montgomery et al. 2016). Deficits in identifying complex emotions in adults with HFA (but not AS) may result from

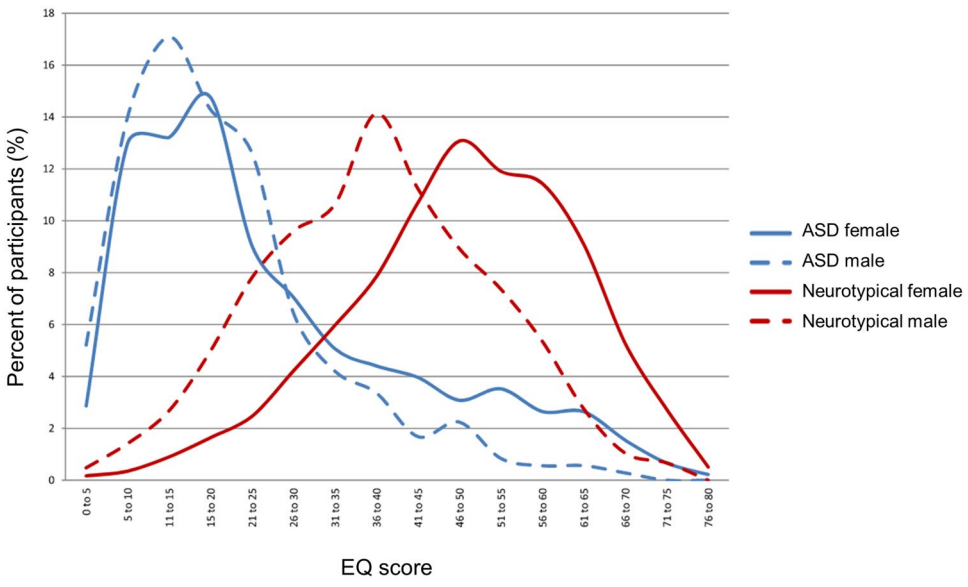

Fig. 4 Characterizing the empathic response in ASD by sex. Distributions of EQ scores are provided for males and females with and without ASD. Individuals with ASD (blue) have lower EQ scores than neurotypical adults (red); males (dashed line) have lower EQ scores than females (solid line) in both comparison and ASD groups. *EQ* empathy quotient, *ASD* autism spectrum disorder Figure modified with permission from Baron-Cohen et al. (2014)

atypical language acquisition that delayed social interactions in early childhood.

ASD comorbidities such as attention deficit hyperactivity disorder (ADHD) and psychosis are also associated with an altered degree of empathy. Compared to children with ASD only, children with combined ASD and ADHD showed increased anxiety, decreased working memory, and less empathy (Colombi and Ghaziuddin 2017). This is clinically relevant since reports suggest that ADHD comorbidities range from 14 to 59% in ASD populations (Goldstein and Schwebach 2004; Keen and Ward 2004). Interestingly, in women with ASD and psychosis, there is an attenuation of the extreme cognitive bias for systemizing over empathizing (Larson et al. 2015). These findings support the theory of an "extreme female brain" that has been proposed for psychosis and mania/hypomania, by which the drive for empathizing is stronger than systemizing (Brosnan et al. 2010).

A quantitative relationship between empathy and ASD severity has been reported by multiple studies that compared cognitive and emotional empathy in individuals with autism, first-degree relatives, and typical individuals (Grove et al. 2014; Sucksmith et al. 2013). Parents (particularly fathers) of children with ASD displayed intermediate impairments in multiple facets of empathy which provides evidence for a subclinical broader autism phenotype (BAP). BAP was also observed in unaffected siblings of children with ASD. These siblings had more subsyndromal autism symptoms compared with healthy children and showed a neurocognitive profile associated with ASD (Eyuboglu et al. 2017). Together, these findings suggest that autistic traits should be measured using quantitative scales and that these traits may be under the influence of genetic or epigenetic factors.

Mechanisms of Empathic Deficits in ASD

Genetic Risk

The BAP observed in relatives strengthens the notion that empathy in ASD is controlled by polygenic inheritance (Abrahams and Geschwind 2008). A review by Betancur (2011) claims that there are over 100 genetic and genomic disorders associated with ASD. A more focused candidate-gene association study found that 19 genes showed a significant association with ASD-relevant behavior traits including empathy (Chakrabarti et al. 2009). Of these genes, GABRB3 (an important gene in the gamma-aminobutyric acid (GABA)-ergic system) has been specifically implicated in ASD and individual differences in empathy (Buxbaum et al. 2002; Warrier et al. 2013). GABRB3 is an important molecule for neuronal growth and differentiation during early development (Ben-Ari et al. 1997; Herlenius and Lagercrantz 2004). GABRB3 also mediates excitatory signaling and variation in *GABRB3* has been associated with the atypical sensory sensitivity in autism spectrum conditions (Tavassoli et al. 2012). Gabrb3 knockout mice even constitute a potential mouse model for autism given their deficits in social and exploratory behaviors (DeLorey et al. 2008).

Genetic variation in the oxytocin system may be another predictor of individual differences in the early development of empathy. Oxytocin is a chemical messenger that controls key aspects of social behavior and social cognition. Oxytocin is important in the formation and maintenance of social relationships and enhances the capacity for empathy (Bartz et al. 2010; Donaldson and Young 2008; Ebstein et al. 2009; Guastella et al. 2009). McDonald et al. (2016) found that a common oxytocin receptor gene (*OXTR*) polymorphism moderated the relation between empathy and the quality of early parent–child interactions in children at risk for ASD. For specific allele carriers, an *OXTR* variant may increase the social salience of interactions, which suggests that taking oxytocin may improve empathic deficits (Green and Hollander 2010).

Neural Network Dysfunction

Since many genes associated with ASD have a role in neural development and connectivity (Chakrabarti et al. 2009), it is not surprising that individuals with ASD have abnormal brain structure and function. In addition to size differences of brain structures that correspond to the extreme male brain theory, individuals with ASD have a reduction in the integrity of long-range white matter fiber tracts (Travers et al. 2012). As one example, Roine et al. (2015) describe local and tract-level white matter abnormalities in the left inferior longitudinal fasciculus (Fig. 5a). These microstructural defects suggest autism is a disconnection syndrome which compromises rapid integration of information across spatially distant brain regions. This results in deficits in social cognition and language (Just et al. 2004; Lewis and Elman 2008). An analysis of resting-state functional connectivity found that deficits of ToM corresponded with reduced connectivity in individuals with ASD (Hoffmann et al. 2016).

Many studies have also examined dysfunctional brain networks that may underlie empathic deficits in ASD. fMRI studies showed diminished fusiform gyrus activation and reduced mirror neuron activity in the inferior frontal gyrus of individuals with ASD. These findings suggest that aberrant mirroring mechanisms underlie empathy impairments in ASD (Dapretto et al. 2006; Greimel et al. 2010; Lassalle et al. 2018). Although the work by Dapretto et al. (2006) is among the most prominent research promoting the broken mirror neuron hypothesis of autism, other research groups were not able to successfully replicate the study's findings (Martineau et al. 2010; Williams et al. 2006). Some recent studies have also challenged the broken mirror hypothesis,

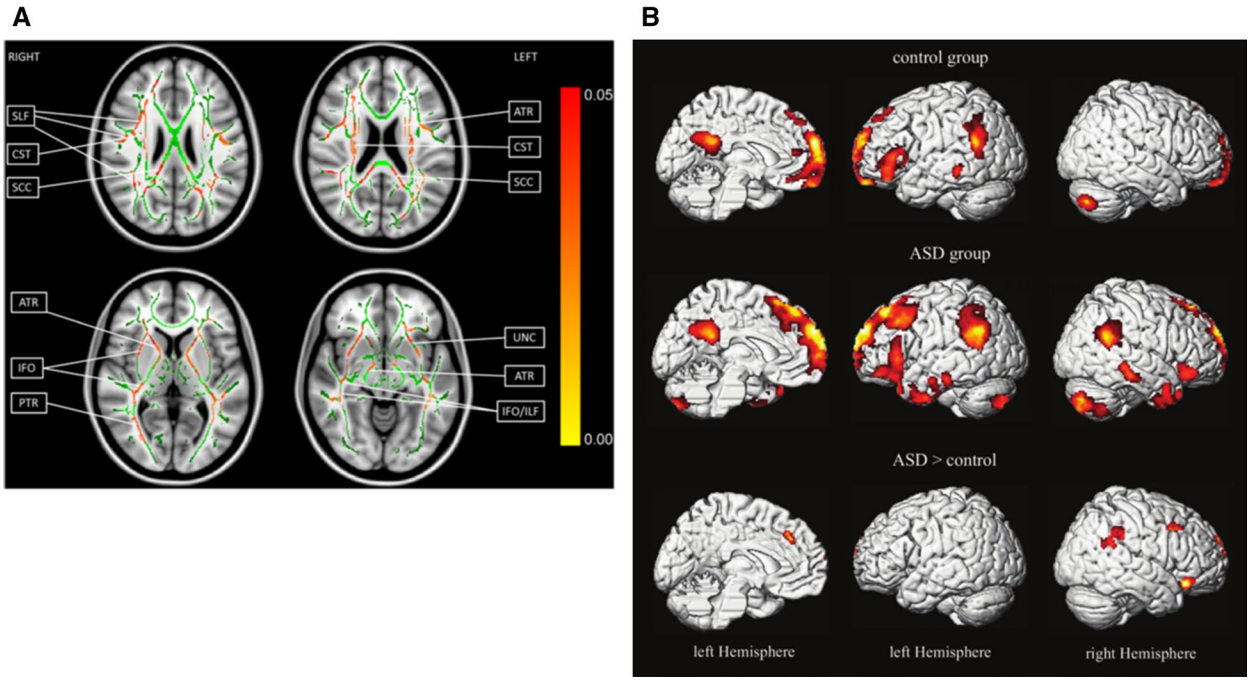

Fig. 5 Abnormal brain structure and function as a mechanism of empathic deficits in ASD. **a** Structural abnormalities in white matter tracts of individuals with AS are shown using constrained spherical deconvolution-based tractography and tract-based spatial statistics. Green color shows the mean fractional anisotropy skeleton calculated from all subjects, and the red color indicates areas of increased fractional anisotropy in individuals with AS (corrected $p < 0.05$). **b** Atypical patterns of neural activation in subjects with ASD were detected using fMRI during an emotional response task (SPMs thresholded at $p < 0.05$). ASD, autism spectrum disorder; *AS* Asperger syndrome, *SLF* superior longitudinal fasciculus, *CST* corticospinal tract, *SCC* splenium of the corpus callosum, *ATR* anterior thalamic radiation, *IFO* inferior fronto-occipital fasciculus, *PTR* posterior thalamic radiation, *UNC* uncinate fasciculus, *ILF* inferior longitudinal fasciculus Figure modified with permission from Roine et al. (2015) and Schulte-Rüther et al. (2011)

suggesting that basic motor mimicry systems are intact in ASD (Schulte-Rüther et al. 2017).

Other network impairments linked to reduced empathic responsiveness in ASD include hypoactivity in the anterior insula and reduced medial prefrontal cortex activation. The former leads to diminished emotional awareness, and the latter creates difficulties in processing cognitive empathy (Fig. 5b) (Klapwijk et al. 2016; Lombardo et al. 2007; Schulte-Rüther et al. 2011; Silani et al. 2008).

In another study by Bellebaum et al. (2014), results demonstrated that individuals with ASD had altered reward system functioning. The processing of social rewards such as making eye contact and looking at pleasant faces occurs in the orbitofrontal and anterior cingulate cortices and involves the dopaminergic system. By measuring event-related potentials, researchers observed that subjects with ASD exhibited a general reduction in feedback-related negativity amplitude which suggests that there are deficits in fast reward processing in ASD (Bellebaum et al. 2014). Deficits in reward processing underlie the social motivation hypothesis of autism and may explain the hyporesponsiveness of individuals with ASD to human faces (Delmonte et al. 2012; Nomi and Uddin 2015; Scott-Van Zeeland et al. 2010). As a result, the extraction of emotion from facial expressions may be more difficult, contributing to ASD deficits in mimicry, empathy, and related processes (Clark et al. 2008; Rigby et al. 2018).

Atypical Sensory Processing

As an extension of abnormal neural networks, various sensory processing deficits are also observed in individuals with ASD. It has been well established that individuals with ASD experience altered sensory reactivity to touch or sound (Marco et al. 2011). Studies on empathic pain responses have shown that people with ASD have difficulties embodying others' pain, suggesting that empathic deficits involve reduced sensorimotor resonance (Minio-Paluello et al. 2009). Sensorimotor resonance reduction is caused by the underactivation of mirror neuron systems and is linked to the absence of embodied empathy (Oberman and Ramachandran 2007; Williams et al. 2001).

Interestingly, Chen et al. (2017) found that although individuals with ASD have lower pain thresholds than neurotypical adults, they show reduced responsiveness to others' pain. The overreaction to sensory stimuli is linked to abnormally high emotional arousal. This causes individuals with

ASD to feel overwhelmed and exhibit dysregulated behavior (e.g., empathic deficits) (Gu et al. 2015). Another study showed that the empathic response to others' pain improves over time but only after being imitated. This suggests that abnormal control over self-other distinction in ASD may underlie empathy deficits (De Coster et al. 2017). Similar to imitation, Koehne et al. (2016) demonstrated that perceived interpersonal synchrony (coordinated action with another individual) increases cognitive empathy in ASD during a finger tapping communication task.

Auditory problems have also been widely linked to ASD and offer a possible explanation for empathic deficits (Rosenhall et al. 1999). Although hearing may appear normal in children with ASD, they process sound differently. Researchers discovered that children with ASD had reduced otoacoustic emissions at the 1 kHz mid-frequency range, which impairs the ability to recognize speech (Bennetto et al. 2017). In addition to this inner ear deficiency, children with ASD can be hypo-or hypersensitive to certain frequencies and volumes of sound. This sensitivity limits their ability to speak and empathize (O'Connor 2012). Therefore, studies examining the intolerance of noise are as important as research on social ineptitude.

Interestingly, studies on adult victims of aphasia following stroke or head trauma found that an acquired loss of language led to social withdrawal and empathic deficits (Hillis and Tippett 2014; Leigh et al. 2013; Yeh and Tsai 2014). Hillis and Tippett (2014) and Yeh and Tsai (2014) concluded that right hemisphere stroke survivors had greater impairment of ToM and empathy. Other studies reported severe depression and incomprehensible emotional outbursts (in addition to the loss of emotional empathy) following aphasia (Code et al. 1999). Auditory impairment and difficulties in processing speech may contribute to empathic deficits in ASD.

Recently, a link between interoception, emotion, and empathy has been investigated in the context of ASD (Mul et al. 2018). Interoception is a sense of the internal state of the body and is important for maintaining homeostasis and aiding in self-awareness (Barrett and Simmons 2015; Craig 2002). Mul et al. (2018) found that individuals with ASD showed a reduction in interoceptive sensitivity and awareness, which correlated to alexithymia (the inability to identify and describe emotions in the self) and empathy. Hence, interoceptive processing should be considered when diagnosing and treating individuals with ASD.

New Diagnostic Tools

Studies show that physiological responses to social stimuli could be biomarkers for autistic traits and social abilities. Truzzi et al. (2016) found that distinct responses in heart rate and facial temperature underlie autistic and empathy traits. Another study used skin conductance to measure resting arousal levels in adults with ASD. Subjects with significantly lower resting arousal performed worse in emotion recognition, judgments of trustworthiness, and cognitive and affective empathy (Mathersul et al. 2013). Recently, Yoshimura et al. (2018) demonstrated that a neurophysiological marker called the mismatch field (MMF) reflects changes in the empathy quotient of adult males with ASD. The MMF is used for the automatic detection of changes in auditory stimuli. However, a larger experimental sample should be used to replicate these preliminary findings before MMF evoked by social voice can become a useful neurophysiological state-dependent marker of empathic abilities. Biomarkers could provide a more objective, reliable, and faster measure of diagnosing ASD in the clinical setting.

While there are abundant screening tools and diagnostic instruments for ASD (e.g., Autism Diagnostic Observational Schedule (ADOS), Autism Diagnostic Interview-Revised (ADI-R), Screening Tool for Autism in Toddlers and Young Children (STAT)), empathy is primarily assessed using the Empathy Quotient (EQ) and the Interpersonal Reactivity Index (IRI). Although the EQ focuses purely on empathy, unlike the IRI, it does not differentiate between cognitive and emotional empathy (Baron-Cohen and Wheelwright 2004; Davis 1983; Rogers et al. 2007). A recently developed tool that may add value to current self-report instruments is the Client Emotional Processing Scale-Autism Spectrum (CEPS-AS) (Robinson and Elliott 2016). The CEPS-AS is administered by observers to measure emotion recognition, self-reflection, cognitive empathy, and affective empathy. The tool showed good interrater reliability with high interdimension associations when used by experienced autism practitioners in the study. However, the level of training required for naïve raters should be assessed before the widespread use of the CEPS-AS.

Another tool that has been developed to assess empathic components is the picture-based Multifaceted Empathy Test (MET) (Dziobek et al. 2008). The MET consists of a series of photographs depicting people in emotionally charged situations. Subjects are required to infer the peoples' mental states (cognitive empathy) and rate their own emotional reactions in response to the pictures (emotional empathy). While the MET demonstrated highly satisfactory convergent and divergent validity as a diagnostic tool, using video format over still pictures could provide better visualization of an emotionally charged situation. When developing new screening or diagnostic tools it is important to consider their applicability across different languages and cultures, and validate translated versions accordingly (Lepage et al. 2009).

Novel Therapies

Since there is no known cure for autism, the main goals of treatment are to lessen associated deficits, to improve quality of life, and to improve functional independence. Current therapies include special education programs, behavioral therapy, and medical management (e.g., drugs, supplements, diets) to relieve associated sleep disturbances, irritability, and hyperactivity. While current pharmaceuticals do not target the core symptoms of ASD, it has been proposed that oxytocin could improve social-communicative deficits (Young and Barrett 2015). However, the efficacy of long-term oxytocin administration remains controversial. Some studies have reported significant improvements in social cognition and empathy (Althaus et al. 2015; Preckel et al. 2016; Preti et al. 2014), while other studies showed no such improvement (Anagnostou et al. 2012; Guastella et al. 2015). Large-scale randomized clinical trials are needed to determine whether oxytocin is a viable treatment option and to establish the optimal dose, method, and frequency of administration.

Generally, improved vocabulary and executive function increase empathic responses. This highlights the importance of therapies that target language and cognitive abilities (Cascia and Barr 2017). Recently, a randomized control trial with 135 children with ASD demonstrated that Theory of Mind training improves empathic responsiveness (Holopainen et al. 2018). Intervention techniques that targeted how to express empathy verbally were also effective (Koegel et al. 2016). In young children with ASD, play-based early intervention programs such as the Early Start Denver Model (ESDM) and the JASPER model have been successful in improving empathy through the development of social, language, and cognitive skills (Dawson et al. 2010; Goods et al. 2013). A randomized trial even concluded that early behavioral intervention using ESDM is associated with normalized brain activity (Dawson et al. 2012). Other interesting therapies that are used to promote emotion inference and empathic responsiveness in ASD include imitation- and synchronization-based dance, puppet vignettes, and equine interactions (Koehne et al. 2016; Malcolm et al. 2017; Schrandt et al. 2009). However, these studies had limited sample sizes and may not be generalizable. Individuals with HFA and AS also benefit from therapy as it improves their communication skills, ability to interact in social settings, and their ability to apply any special interests in day-to-day life (Golan and Baron-Cohen 2006).

Discussion

Methodological Limitations

This review describes empathy in ASD, highlighting clinical characteristics, the mechanisms that cause empathic deficits, and the emergence of new diagnostics and therapies. PubMed, PsycINFO, and Embase databases were specifically selected to focus the search on clinically relevant studies that might inform clinical and research practices. The use of these databases introduces selection bias towards the 61 studies that were reviewed. Relevant articles from related areas (e.g., sociology, cultural anthropology) were not likely to be identified using the search criteria. The search only included articles that had the terms "empathy" and "autism" or "Asperger" or "autism spectrum disorder" in the title. A rigorous screening process was implemented to ensure that the studies focused specifically on empathy in ASD, and not on broader concepts of social cognition and emotional processing.

Mixed Subject Populations

Another limitation of the reviewed studies was the lack of homogeneity among subject groups. Before the release of the DSM-5, autism and AS were separate diagnoses. The reclassification of subtypes into the broader diagnosis of ASD resulted in heterogeneous study populations. Furthermore, there is no robust body of evidence to support diagnostic distinctions between AS and HFA. If individuals with AS or HFA have the same developmental level or IQ, their clinical response to treatments is similar, even though autism has early language delays and AS does not (Howlin 2003). There is also mixed evidence on whether people with AS or HFA perform differently on tasks examining ToM, verbal and performance IQ, clumsiness, or executive functions (Barbaro and Dissanayake 2007; Klin et al. 1995; Rinehart et al. 2006a, b; Thede and Coolidge 2007; Verté et al. 2006).

Consequently, the studies examined for this review involved mixed subject populations. Generalized ASD involves individuals with LFA, HFA, and AS, whereas high-functioning ASD includes both HFA and AS. While studies with mixed patient populations represent the entire autism spectrum per the new diagnostic criteria, it is difficult to achieve conclusive results given the large variation in cognitive abilities and social communication skills.

The studies examined in this review do not mix child and adult subject population, due to the differences in the diagnosis of autism in children versus adults. Language deficits are among the most serious problem for children diagnosed with autism whereas adults do not require these language deficit criteria for a diagnosis. Individuals diagnosed with autism in adulthood might have had milder symptoms when young and some capacity to develop adaptive skills and behaviors. Thus, the diagnosis of autism in adulthood cannot be considered the same disorder as that described by Kanner in 1943.

Studying homogeneous subgroups could decrease variation. Subgroups can be defined based on the level of

intellectual disability (i.e., low- vs high-functioning autism) or risk factors such as sex, environmental exposures (e.g., air pollution, organophosphates, heavy metals), and genetic mutations (Betancur 2011; Herbert 2010; U. S. Department of Health and Human Services 2012). Heterogeneity could also be addressed by examining the relationship between empathic responses and clinical features on a continuum.

Selective Subject Populations

While the variation along these clinical dimensions is of interest, studying empathy in ASD is challenging because performing empathy tasks is difficult in individuals with a low IQ. Given that empathy requires intellectual ability and language, many of the examined studies only included subjects with AS or HFA. Despite the predominance of intellectual disability in ASD (Newschaffer et al. 2007), many studies selected higher-functioning participants. This controlled the level of understanding of instruction between ASD and comparison groups and allowed subjects to complete online tasks and self-report their clinical diagnoses (Baron-Cohen et al. 2015; Chen et al. 2017; Rogers et al. 2007). Even though the most serious problem for children with autism is the failure of language development, all research subjects had language in order to follow study instructions. Thus, it remains uncertain whether the research findings from these studies would generalize to subgroups with intellectual disabilities (i.e., LFA).

Informing Clinical and Research Practices

The current research on empathy in ASD is extensive and includes studies that characterize the effects of sex, age, IQ, disorder severity, and comorbidities on the empathic response of individuals with ASD. Mechanisms that underlie empathy are being researched and include studies on genetics, neural networks, and sensory processing. Together, an understanding of the clinical characteristics and potential mechanisms of empathic deficits in ASD will better inform future studies and lead to improved diagnostics and therapies.

Important distinctions have already been made in the empathic response of males and females with ASD, and in individuals with associated ADHD or psychosis. Adopting a multidimensional approach to differentiate between cognitive and affective empathy will be of great value to uncover the complexities of empathy in ASD. Similarly, it will be important to determine the extent to which studies on high-functioning individuals with ASD translate to those with LFA.

As research in empathy and ASD continues to develop, we can expect to gain a better understanding of the mechanisms underlying empathy in ASD. Such knowledge is critical to improving the social communication and social interactions of individuals with ASD.

The Future of Empathy in ASD

The current understanding of the concept of empathy in ASD remains limited by the oversimplification of the complex nature of ASD. While classifying autism and its related neurodevelopmental disorders on a spectrum has led to improvements, a personalized approach to characterizing ASD may be more useful. Since precision medicine is expected to become the future of healthcare, it will be important to consider specific risk factors, genetic phenotype, pharmacokinetic characteristics, and other features unique to individuals with ASD (Chen and Snyder 2012). Since empathic deficits may arise from abnormal genetics, neural networks, and sensory processing, studies should explore epigenetics and the interaction between environmental factors and genetic susceptibilities. Care could be optimized for individuals with ASD by developing therapies that use prognostic or predictive biomarkers and genetic testing (Loth et al. 2016).

To advance the next generation of theories of empathy in ASD, societal changes in the modern world need to be considered. Evidence suggests that there has been a decrease in empathy (and an increase in narcissism) in the last two decades among neurotypical individuals (Konrath et al. 2010). It has been hypothesized that this trend is due to the increased use of technologies, especially social media use, which decreases face-to-face interaction and promotes self-interest (Alloway et al. 2014; Misra et al. 2014). Other societal changes that are related to rising narcissism (and declining empathy) include increases in individualism, self-esteem, and positive self-views (Twenge and Campbell 2001, 2008). By definition, individualistic people are more concerned with their well-being and success than those of others. The rise of materialism and social isolation are both related to decreased prosocial behavior, which is a major aspect of empathy (Kasser and Ryan 1993; Twenge et al. 2007; Vohs et al. 2006). Understanding the implications that these societal factors have on empathy in neurotypical individuals may inform interventions and therapies for ASD.

Conclusion

This review provides a detailed account of empathy in the context of clinical characteristics of individuals with ASD, the mechanisms that cause empathic deficits, and the emergence of new diagnostics and therapies. Issues that have emerged from reviewing articles on empathy in ASD include the presence of mixed and selective subject populations and translating research into practice. These issues limit our

current understanding of empathy and the treatment of individuals with empathy deficits. The interplay of multiple risk factors underlying empathic deficits in ASD will need to be studied to deliver personalized care and optimize individual treatment plans.

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Conflict of interest The author declares that she has no conflict of interest.

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