OPINION

The dog (*Canis familiaris*) as a translational model of autism: It is high time we move from promise to reality

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Selecting appropriate animal models for a particular human phenomenon is a difficult but important challenge. The difficulty lies in finding animal behaviors that are not only sufficiently relevant and analog to the complex human symptoms (face validity) but also have similar underlying biological and etiological mechanisms (translational or construct validity), and have "human-like" responses to treatment (predictive validity). Over the past several years, the domestic dog (*Canis familiaris*) has become increasingly proposed as a model for comparative and translational neuroscience. In parallel to the recent advances in canine behavior research, dogs have also been proposed as a model of many human neuropsychiatric conditions, including autism spectrum disorder (ASD). In this opinion paper we will shortly discuss the challenging nature of autism research then summarize the different neurocognitive frameworks for ASD making the case for a canine model of autism. The translational value of a dog model stems from the recognition that (a) there is a large inter-individual variability in the manifestation of dogs' social cognitive abilities including both high and low phenotypic extremes; (b) the phenotypic similarity between the dog and human symptoms are much higher than between the rodent and human symptoms; (c) the symptoms are functionally analogous to the human condition; and (d) more likely to have similar etiology.

This article is categorized under:
    Psychology > Comparative Psychology
    Cognitive Biology > Evolutionary Roots of Cognition

KEYWORDS
autism spectrum disorder, dog, model, translational validity

1 | INTRODUCTION

The application of a comparative approach is one of the emerging trends in research on different aspects of human behavior and cognition. In the context of these changes, the domestic dog (*Canis familiaris*) has become increasingly popular in various fields of comparative research ranging from genetics and molecular biology (Switonski, 2014) to social cognition (Bensky, Gosling, & Sinn, 2013) and psychology (Payne, Bennett, & McGreevy, 2015). The rapidly *blossoming interest* among *researchers* in canine behavior and (social) cognition stemmed from the recognition that the dog is unique among domesticated species not only because they share an evolutionary and developmental history with humans by living in and adapting to a similar social environment (Hare, Brown, Williamson, & Tomasello, 2002) but also because this evolutionary adaptation caused marked changes in the dogs' socio-cognitive functioning (Miklósi & Topál, 2013). Ample evidence indicates that there

is extensive similarity and functional overlap between dogs and human children in a set of shared behavior traits (e.g., Horn, Huber, & Range, 2013; Kaminski, 2009). In parallel with the recent increase in scientific interest in canine behavior and cognition, the domestic dog has gradually become a rising star in translational research addressing many aspects of human health. Dogs are increasingly recognized as a model for age-related cognitive impairments (Champagain, Range, Huber, & Virányi, 2018), other neurological disorders (e.g., Alzheimer's disease, Van Dam & De Deym, 2011), various non-neurological diseases (e.g., diabetes, Adin & Gilor, 2017) and obesity (Pogány et al., 2018). In addition, many of the human psychiatric disorders have apparent canine analogs (Ledford, 2016; Overall, 2000) and canine epilepsy has also been proposed as a promising comparative model for human epilepsy (E. E. Patterson, 2014). Importantly, canine and human diseases are not only remarkably similar in terms of phenotypic manifestation, but in many cases, also share causative genes and respond to treatment in similar ways (Araujo et al., 2011; Parker, Shearin, & Ostrander, 2010).

Together, these findings suggest that the domestic dog serves as an ideal and natural model of comparative and translational neuroscience (Bunford, Andics, Kis, Miklósi, & Gácsi, 2017) and this model organism may offer higher translational value than other commonly used laboratory animals such as rats and mice. Moreover, dogs have adapted to anthropogenic environment where the canine disease conditions appear spontaneously or endogenously without genetic or neurochemical manipulation, thus providing an opportunity for higher *face validity* (similarity in the phenotypic expression of the symptoms), and *construct validity* (similarity in the basic underlying mechanism responsible for the condition in humans). All in all, dogs offer a unique opportunity to explore the underlying neural and genetic structures and environmental correlates of numerous human diseases. Capitalizing on advantages of the dog as a translational model of complex human phenotypes, the present paper focuses on how (and why) the domestic dog can contribute to our better understanding of human autism spectrum disorder (ASD).

2 | THE CHALLENGING NATURE OF AUTISM RESEARCH

Autism is a neurodevelopmental disorder that has received considerable interest in recent decades due to the rapid and ongoing rise in its prevalence in Western countries (Baxter et al., 2015; Centers for Disease Control and Prevention, 2018; Siniscalco, Bradstreet, & Antonucci, 2013). For example, ASD prevalence was 0.67% in 2000 and 2.76% in 2016 among US adults and children (Xu, Strathearn, Liu, & Bao, 2018). Despite extensive research, the pathogenesis of autism is still largely unknown and there is a compelling need to deepen our understanding of this disorder, including with regard to etiological and maintaining characteristics of symptoms as well as associated functional impairments. The key challenge in exploring these research questions lies in the fact that autism is referred to as spectrum disorders because its symptoms can appear in a number of different combinations and occur along a continuum of severity. ASD is characterized by persistent deficits in two core domains that have to be present in the early developmental period: (a) socio-communicational dysfunctions (i.e., deficits in communicative behaviors, impaired social reciprocity, and poor interactional and emotional synchrony) and (b) restricted, repetitive patterns of behavior (i.e., stereotyped motor movements, narrow, fixated interests and insistence on sameness and routines) (American Psychiatric Association, 2013).

ASD, from an etiological perspective, is not a single pathophysiological entity. The variations in the phenotypic manifestation of ASD are most likely the final outcome of the interactions of multiple genetic and environmental (developmental) factors (Betancur & Coleman, 2013). Concepts such as equifinality and multifinality (Shields & Cicchetti, 1998; von Bertalanffy, 1968) are also important to gain a better understanding of ASD. Namely, from a system-theoretical perspective, ASD is characterized by both equifinality and multifinality; the same end state (formal diagnosis of ASD) may be reached from a variety of different initial conditions and through different processes (equifinality), and at the same time, any one component (predisposing factor) may function differently depending on the organization of the system in which it operates (multifinality). The large developmental and phenotypic plasticity presents a huge challenge for current research on autism. One possible way to overcome this problem is to assume that the effects of heterogeneous genetic and environmental risk factors converge at the intermediate level (in between the low/genetic and high/behavioral levels) of organization of the spectrum disorder. The idea of some common factors at the level of neurocognitive functioning has the potential to yield a more coherent conceptualization of ASD that otherwise seems too heterogeneous and polymorphic to conduct research on. Such neurocognitive endophenotypes (e.g., social attention, Jones, Venema, Earl, Lowy, & Webb, 2017) may constitute a point of convergence for a multitude of genetic and environmental factors (Figure 1).

2.1 | In search for the central neurocognitive factor in autism spectrum

In the past few years different neurocognitive frameworks have been proposed to account for symptoms in ASD. Domain-specific social cognitive theories focus on social cognitive and attentional aspects of ASD suggesting that the core deficit
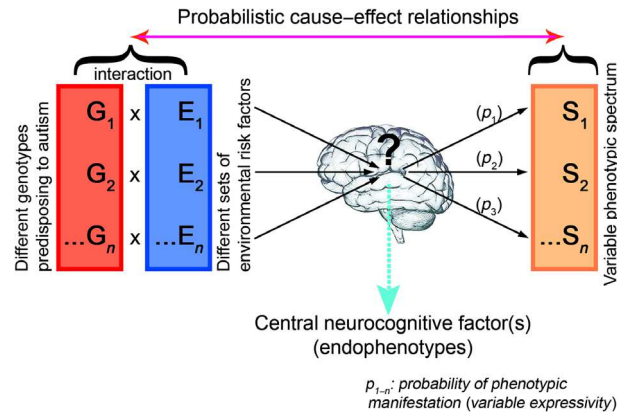
FIGURE 1 Schematic description of the complex etiology of autism spectrum disorder

stems primarily from *impaired social cognition* (Theory of Mind deficit, Baron-Cohen, 2000) while others explain ASD in terms of perceptual and *sensory processing impairments* (weak central coherence, Happé & Frith, 2006; enhanced perceptual functioning, Mottron, Dawson, Soulières, Hubert, & Burack, 2006). More recent approaches, however, focus on *social motivation deficits* as the dominant cause for the development of the social impairments associated with ASD (Chevallier, Huguet, Happé, George, & Conty, 2013). This account suggests that reduced interest and attention to social stimuli in early childhood can deprive the mind of crucial social inputs during the sensitive period for the development of social cognitive abilities, which leads to diminished social cognitive performance later in life. The findings that patients with ASD (a) show no preferential orientation to the socially relevant stimuli (Constantino et al., 2017; Dawson et al., 2004); (b) they are less likely to seek out social contact (Wetherby, Prizant, & Hutchinson, 1998); and (c) in contrast to their intact monetary reward processing (Gonzalez-Gadea et al., 2016) they have deficits in representing the reward value of social interactions (Demurie, Roeyers, Baeyens, & Sonuga-Barke, 2011; Osterling, Dawson, & Munson, 2002) seem to support this idea.

An even more recent account of the mechanisms underlying autistic behavior in humans proposes that many of autism's salient traits may be manifestations of a single underlying impairment of perception of the probabilistic nature of environmental regularities (*atypical tolerance for prediction error*, Hellendoorn, Wijnroks, & Leseman, 2015; Sinha et al., 2014; Van de Cruys, Van der Hallen, & Wagemans, 2017). That is, people with ASD perceive and respond to violations to their predictions atypically due to their "low and inflexible" tolerance for prediction error. ASD subjects' brains are unable to ignore even accidental/irrelevant changes in the environment (i.e., unable to learn to ignore prediction errors) and thus every minor violation induces new learning without gaining a sense of control. Such perception of unpredictability makes people with ASD unable to meta-learn (i.e., learning which features in a task convey learnable regularities and which one can be regarded as meaningless stochastic fluctuations). The findings that subjects with ASD perform well in visual detection and discrimination tasks (Vossel et al., 2014) but their executive attention is atypical, and they often miss the point (Elison et al., 2013) seem to support their difficulties in meta-learning. Although the above explanatory approaches focus on different aspects of neurocognitive functioning and attempt to explain autism at different levels of neurocognitive processing, these accounts are not necessarily mutually exclusive, but rather offer complementary approaches in ASD research.

3 | TRANSLATIONAL APPROACHES TO UNDERSTAND AUTISM: POTENTIALS AND LIMITATIONS

The fact that both proximate and ultimate mechanisms underlying the development of the autistic behaviors remain to be refined poses an acute problem for autism research, and stresses the need for animal models that may advance our understanding of the disease mechanisms. The traditional rodent models boast an impressive array of experimental evidence (Lazaro & Golshani, 2015), the molecular genetics models of ASD are precise and tractable (Watson & Platt, 2012) and some of the core features of human autism can be simulated in mice (Bicks, Koike, Akbarian, & Morishita, 2015). Importantly, however, this approach suffers from significant limitations. One major concern is that there are substantial differences between humans and rodents with regard to the natural social behavior and social structure. Rats and mice lack the complexity of human social behavior and this, among others, bears the risk of drawing oversimplified parallels between human and rodent behavior. Moreover, several characteristics of ASD—typically those which require higher level of social cognitive functioning—are difficult or impossible to study in rodents (P. H. Patterson, 2011) and the wide range of ASD symptoms that occur spontaneously in humans must be experimentally induced in these animals (e.g., Nicolini & Fahnestock, 2018). Thus, while rodent models of

ASD can undoubtedly advance our understanding of the basic behavioral regulatory mechanisms (Watson & Platt, 2012) the greatly dissimilar nature of human and rodent social cognition (i.e., the set of mental operations and the social communicative signals that are used in social interactions with others—Millan & Bales, 2013) seriously restricts the impact of rodent models on understanding the complex social cognitive aspects of human ASD.

Although no animal model can fully mirror the various phenotypic expressions characteristic of human ASD, higher degree of similarity between human and nonhuman natural behavior repertoire—particularly as regards behaviors that serve a social communication function—is a powerful tool for increasing face and construct validity thereby increasing the translational capacity of the animal model. In line with this idea, many assume that the use of nonhuman primate models allows a closer approximation of ASD symptomatology (Watson & Platt, 2012). However, it is noteworthy that despite the obvious benefits to study rhesus monkey models of ASD (Bauman & Schumann, 2018), these models may be of limited value in studying some of the core social communicative symptoms. For example, eye contact is linked mainly to affiliative and information sharing motivations in humans and it has an important role in ostensive communication (Csibra, 2010). In contrast, prolonged eye contact in nonhuman primates serves primarily as a threat to the conspecifics (Gomez, 1996) and has little (if any) communicative significance (Kano et al., 2018). Recent research has shown, however, that despite the distant evolutionary relationships between dogs and humans, domestic dogs use eye contact and gazing in interspecific situations (towards humans) in a human(infant)-like manner (Topál, Kis, & Oláh, 2014). Moreover, compared with nonhuman primates studied mainly in captivity and under semi-natural conditions, dogs, like human children, can be observed in their natural environment and/or can be tested in a less restrictive way (see e.g., the eye-tracking experiments with head-unrestrained dogs, Téglás, Gergely, Kupán, Miklósi, & Topál, 2012). Even more importantly, the experimental paradigms for studying dogs' social skills are well-matched (or even identical) to those used to assess children's social skills. This uniquely positions the dog model to bridge the gap between nonhuman primate models and human ASD populations.

It is also important to consider whether or not the dog model can be used to study human ASD symptoms across the developmental spectrum. Based on the notion that one of the consequences of dog domestication is the retention of juvenile and puppy-like behavioral traits into adulthood (paedomorphism, Goodwin, Bradshaw, & Wickens, 1997), and at least prima facie, dogs' cognitive developmental level is more comparable to children's than to adults', it seems reasonable to assume that the dog serves as a suitable model of children with ASD. However, human ASD is a lifelong condition, and diagnosis is generally stable over time (Lord et al., 2006) even though longitudinal studies indicate the possibility of improvement in symptoms with age (Bal, Kim, Fok, & Lord, 2018). Therefore, we may suppose that the dog can serve as a model for studying ASD symptoms predominantly, but not exclusively, in children.

Increasing evidence suggest that domestic dogs represent the ideal subjects for studying the genetics of social behavior (Jensen et al., 2016) and the evolution of a human-analog social competence (Miklósi & Topál, 2013). In line with this idea, recent genetic studies have identified candidate genomic regions associated with human-directed social behaviors in dogs (Kis et al., 2014; Persson, Wright, Roth, Batakis, & Jensen, 2016) and an experimental investigation of behavioral variations within a certain breed (Bull Terrier) revealed behavioral and endocrine phenotypes similar to the clinical presentation of human autism (Tsilioni et al., 2014). Namely, tail chasing in Bull Terriers may serve as an indication of autism-like behaviors: this stereotypical behavior is closely associated with owner-directed explosive aggression, trancing, social withdrawal and persistent preoccupation with objects. In addition, tail-chasers are also unable to cope with stressful situations and males are affected more often than females (Moon-Fanelli, Dodman, Famula, & Cottam, 2010). Results from a dog owner survey on the social behaviors of Miniature and Standard Poodles also indicated autism-relevant behaviors in smaller subgroups of these breeds (Zamzow, Lit, Hamilton, & Beversdorf, 2017). We should also note that the potential link between individual differences in ASD-like behaviors in dogs and (social) learning performance is an intriguing yet understudied field. It has been shown, for example, that puppies that react negatively to being petted by a human handler are more likely to be withdrawn from the guide dog training program than more sociable subjects (Asher et al., 2013) and dogs that show predisposition towards stereotypic behaviors differ from the normal population in terms of their cognitive flexibility (i.e., they show greater resistance to extinction in a reversal learning task, Protopopova, Hall, & Wynne, 2014).

These preliminary results hold promise for the use of the dog as a novel model system for human social disorders in general (vonHoldt et al., 2017) and for ASD in more particular (Persson et al., 2016). It is important to note, however, that not only genetic and neuroendocrine factors contribute to the symptoms of ASD, but neurocognitive functions also play a pivotal role in the regulation of core behaviors.

Here we propose that in order to adapt to living in human social environment, dogs' neurocognitive functions underwent a series of changes affecting a wide array of social features in this species. This led to the emergence of human(infant)-analog social competence in dogs (Miklósi & Topál, 2013; Topál, Gergely, Erdőhegyi, Csibra, & Miklósi, 2009; Topál et al., 2009; Topál et al., 2014) and, as a consequence of these specific changes, the dog as a model organism for ASD presents a promising alternative to the commonly used rodent models. Accordingly, we may assume that (a) there is a large inter-individual

variability in the manifestation of dogs' social cognitive abilities including both high and low phenotypic extremes; (b) the phenotypic similarity between the dog and human symptoms are much higher than between the rodent and human symptoms; (c) the symptoms are functionally analogous to the human condition; and (d) more likely to have similar etiology.

4 | DOGS CAN UNIQUELY MIMIC THE KEY NEUROCOGNITIVE ASPECTS OF HUMAN ASD

Based on the above considerations, we may assume that the convergent evolution of human and dog social cognition (Hare et al., 2002; Topál, Gergely, et al., 2009; Topál, Miklósi, et al., 2009) has led to the emergence of human-directed social competence in dogs (Bräuer, Kaminski, Riedel, Call, & Tomasello, 2006; Hare et al., 2010; Miklósi & Topál, 2012) that make this animal a powerful model for autism research (Table 1). This may be especially true when studying the key neurocognitive aspects of human ASD including *social motivation deficit* (Chevallier et al., 2013) and *atypical tolerance for prediction error* (Hellendoorn et al., 2015; Sinha et al., 2014; Van de Cruys et al., 2017) as potentially underlying causes of ASD-like behaviors.

If the behavior symptoms of ASD stem primarily from the dysfunctions of the social affiliative motivation system, the analogs of this system can be found only in species which, during their evolution, faced similar challenges in adapting to the social environment as humans. Importantly, ASD seems to affect specifically the motivation for social affiliative interactions. This motivation can be seen as a distinct category among other types of social motivations (sexual, parenting, etc.—Kenrick, Griskevicius, Neuberg, & Schaller, 2010) and it is associated specifically to the needs of belongingness, affection, social acceptance, and social conformity in people (Over, 2016). Ample evidence suggests that dogs are not only motivated but uniquely competent in interacting with humans and they display many of these social skills specifically towards humans and not towards conspecifics (Topál et al., 2014; Worsley & O'Hara, 2018). It seems that the motivation systems which regulate the social behaviors directed towards conspecifics in dogs are different from those of regulating human-directed social behaviors. This later motivation system may represent a functional analog of the human social-affiliative motivation system and this is a key factor in the development of the dogs' human-like social competence. Human social cues appear to be inherently rewarding for dogs and there are other intriguing parallels between the dogs' human-directed social cognitive behavior and the behavioral manifestations of the human social-affiliative motivation systems (Gácsi et al., 2005; Miklósi et al., 2003). A possible consequence of dogs' "human-tunedness" is that tools that can keep dogs and young children motivated in experimental settings are very similar, and these tools are quite different from those used in rodent or primate experiments. Although food rewards can be an effective way to encourage both rodents' and dog' participation in experimental trials, dogs (unlike wolves, see Feuerbacher & Wynne, 2012) are generally highly responsive to social reinforcement such as stroking or verbal praise. This factor plays a crucial role in experimental designs aimed to manipulate or measure phenomena relevant to social motivation.

Moreover, the oxytocin system, like in humans, plays a key role in modulating human-oriented social behaviors in dogs (Kis et al., 2017; Nagasawa, Ogawa, Mogi, & Kikusui, 2017; Somppi et al., 2017). Although the expression of these behaviors is a general characteristic of the domestic dog, there are considerable variations between individuals as well as between breeds (Kovács, Kis, Pogány, Koller, & Topál, 2016). Compared to the currently available rodent models, the abnormal expression of these behaviors in dogs could be more relevant to the human ASD symptoms regarding both the phenotypic similarity and the etiology.

The dog model also offers high translational value if we accept that atypical perception of discrepancy between the actual and expected outcome (prediction error) is a fundamental deficit in ASD. This is so because, in response to challenges of adaptation to human environment, dogs have evolved a highly flexible information processing system. That is, human social settings provide a wide variety of cognitively demanding inputs for dogs and thus the development of social competence in dogs in such a complex social environment largely depends on whether signals (i.e., learnable regularities) and noise (i.e., "meaningless" deviations from predictions) are properly disentangled. Dogs often participate in noisy and dynamic social interaction scenes during which they (like young children) can efficiently generate adequate "social scripts" (e.g., social rules, Topál, Kubinyi, Gácsi, & Miklósi, 2006) that can be applied broadly in adequate social contexts. Domestic dogs acquire such meta-knowledge more flexibly than their wild ancestors (Topál, Gergely, et al., 2009) and this social learning aptitude implies flexible tolerance for prediction error during information processing. We may assume, however, that there are considerable individual (and/or breed) differences in dogs' ability to extract meta-knowledge from complex social interactions with humans. If a dog perceives and responds to violations to its predictions atypically due to its "low and inflexible" tolerance for prediction error, this may manifest as atypical use of eye contact, emotion recognition deficits etc. (i.e., deficits that parallels that of children with autism). Importantly, a systematic (and direct) investigation of the relevance of these concepts in ASD-like animal behaviors is still missing from the literature.

TABLE 1 Selected examples of the parallels between behavioral manifestations of autism spectrum disorder (ASD) and potentially relevant human-analog social cognitive skills in dogs

Behavioral manifestation	Human studies		Studies on dogs	
	Findings (behavior of patients with ASD as compared with typically developing participants)	How it is measured? (References)	Findings (potentially ASD-relevant human-analog social cognitive skills)	How it is measured? (References)
Preference for face-to face interactions and eye contact	Infants with ASD look at the face of another less often	Coding of home video tapes of the infants' first birthday party (Osterling et al., 2002).	Even 5-week-old puppies show a spontaneous tendency to gaze at the human's face (increased preference for face-to-face interactions)	Dogs are allowed to explore an unfamiliar room freely in the presence of non-interactive human partners (Gácsi et al., 2005)
	Adolescent individuals with ASD made fewer fixations on the eye region of faces	Watching video clips of social interactions (eye-tracking technology) (Klin, Jones, Schultz, Volkmar, & Cohen, 2002)	Adult pet dogs visually explore the eye-region of human faces more than other facial features	Watching human facial images (eye-tracking technology) (Kis, Ciobica, & Topál, 2017; Somppi, Törnqvist, Hänninen, Krause, & Vainio, 2014)
Understanding of the referential nature of looking	Children with ASD show deficits in initiating and responding to joint attention and gaze shifts (between a person and an object)	Adult–child interactions in a standard but flexible manner (Wetherby et al., 1998)	Dogs readily follow and direct human gaze	Target object is indicated by a human's gaze (either real choice task—Kaminski, 2009 or eye tracking—Téglás et al., 2012)
			Relying on the gaze direction of humans, dogs are able to infer who is commanded to perform an action	Testing dogs' response to their owner's commands. The owner is facing either the dog or a human partner or none of them (Virányi, Topál, Gácsi, Miklósi, & Csányi, 2004)
Production of directional gestures as signals referring to a target object	Infants at high risk for ASD (8–18 months) show slower growth of behavioral requesting (reaching towards or proto-imperative pointing to a desired toy)	Semi-structured interaction with a standardized toy set. Tasks are designed to elicit referential communication through the use of high interest objects (Ibañez, Grantz, & Messinger, 2013)	Dogs possess an impressive repertoire of referential gestural cues to communicate and interact with people	Coding of home video tapes of everyday communicative bouts (e.g., requesting food and doors to be opened, playing, etc.) with humans (Worsley & O'Hara, 2018)
Social referencing (taking cues from others to form one's own responses to certain events)	18-month-old infants at high risk for ASD are less likely to seek information from an adult when confronted with a novel stimulus and exhibit impairments in regulating their behavior based on the adults' emotional signals	Semi-naturalistic play setting: presentation of different toys are accompanied by verbal information (pretty, nasty, ordinary) and emotionally congruent facial expression (Cornew, Dobkins, Akshoomoff, McCleery, & Carver, 2012)	Dogs tend to look referentially at the informant and use the emotional messages to guide their own behavior towards an external object/situation	Dogs are presented with a potentially scary object in the presence of their owner or a stranger. Human informant display either a negative or positive emotional reaction towards the object (Merola, Prato-Previde, & Marshall-Pescini, 2012)
Social learning through imitation	Patients with ASD are more likely to imitate in a structured, elicited situation than an unstructured socially driven context. Imitation impairment in ASD reflects deficits in social communicative functioning rather than problems associated with the instrumental nature of the modeled action	Assessing the ability of participants with ASD to respond on demand to the demonstrations of an unfamiliar experimenter in a controlled laboratory setting (Ingersoll, 2008)	Dogs are able to flexibly imitate human demonstrations (both body-oriented and manipulative actions), even after a delay (deferred imitation) and can generalize imitation across modifications in contexts. They are also able to recognize the goals of others and adjust their behavior accordingly	Dog are trained with the Do as I Do method to match their behavior to demonstrated actions (Fugazza & Miklósi, 2014)
Audience effect (the influence of the mere presence of a human partner on subject's behavior)	Patients with ASD tend to ignore audience expectations (e.g., they are reluctant to change their behavior to the varying requirement of an audience and are not influenced by the presence of an observer when making donations)	Participants are asked to describe themselves when specific information is given about the audience preferences (Scheeren, Begeer, Banerjee, Meerum, & Koot, 2010), or in a dictator game, participants are asked to make charitable donations in the presence or absence of observers (Izuma, Matsumoto, Camerer, & Adolphs, 2011)	Dogs tend to conform to a human's expectations (e.g., do not eat the forbidden food) in the presence (vs. absence) of an attentive human, and show appeasing behaviors (guilty look) when scolded for supposedly eating a forbidden treat	A piece of food is placed on a plate and the experimenter forbids the dog from taking it. The dog is either left alone for a while or a human remains present (Kaminski, Pitsch, & Tomasello, 2013; Hecht, Miklósi, & Gácsi, 2012)

(Continues)

TABLE 1 (Continued)

Behavioral manifestation	Human studies		Studies on dogs	
	Findings (behavior of patients with ASD as compared with typically developing participants)	How it is measured? (References)	Findings (potentially ASD-relevant human-analog social cognitive skills)	How it is measured? (References)
Emotion recognition and emotional synchronization	Patients with ASD have lower success in recognizing human facial emotions and in matching different modalities of emotional expressions	Participants are asked to assess emotions from photographs of faces (Bormann-Kischkel, Vilsmeier, & Baude, 1995) or to match pictures of facial expressions with videotaped gestures and vocalizations (Hobson, 1986)	Dogs are sensitive to emotions expressed in human faces	Dogs are trained to discriminate between photographs of their owner's positive and neutral facial expressions (Nagasawa, Murai, Mogi, & Kikusui, 2011) or using eye tracking technology to observe dogs' reaction to pictures of human faces (Barber, Randi, Müller, & Huber, 2016)
	Children with ASD demonstrate less frequent emotional responsivity and emotion contagion in reaction to positive and negative emotional displays	Experimenter displays different affects (e.g., joy, fear, disgust) in different situations (e.g., opening a small gift box and reacting to the content) (Scambler, Hepburn, Rutherford, Wehner, & Rogers, 2007)	Dogs are able to distinguish between different positive and negative emotions conveyed by human faces and sounds. They also show emotional contagion in response to negative sounds or facial expressions from humans	Dogs are presented with pairs of different facial expressions and/or emotionally charged human sounds (Albuquerque, Guo, Wilkinson, Resende, & Mills, 2018; Huber, Barber, Faragó, Müller, & Huber, 2017)
Social conformity (susceptibility to social influence)	Children with ASD conform less to the misleading opinion of others	Participants are asked to indicate which one of cartoon figures a comparison figure matches in size and they receive either misleading or correct information about other people's opinions (Yafai, Verrier, & Reidy, 2014)	Dogs spontaneously adopt a seemingly pointless behavior (making a short detour) by observing their owners' habitual behavior	Longitudinal observations of dog walkers: owners are asked to form a new habit—making a short detour before entering the house (Kubinyi, Miklósi, Topál, & Csányi 2003)
			Dogs show a tendency to conform to the human's choice even when it is counterproductive (e.g., they ignore their natural preference for the larger amount of food)	Quantity discrimination task: a choice between large and small food quantity. After the "no influence" trials dogs are allowed to choose only after observing the experimenter expressing a preference for the smaller quantity. (Marshall-Pescini, Prato-Previde, & Valsecchi, 2011; Prato-Previde, Marshall-Pescini, & Valsecchi, 2008)

5 | CONCLUSION

Despite extensive research over past decades, the neurocognitive mechanisms of autism are still poorly understood and there remains a need to promote conceptual understanding of this unique human disorder. In this study, we make the case for a novel translational approach to study ASD, arguing that the dog naturally serves as a model for understanding different aspects of human social behavior and cognition including the core symptoms of autism. Evidently, however, more research is needed to explore the translational value of dog models. The most compelling task for future research is to bring together cutting-edge neuroscience and genotyping methods with behavior phenotyping, in order to compare humans' and dogs' social behavior and the underlying neurobiological mechanisms. Studying the relationship between different aspects of social behavior and the oxytocin system in the dog is also a promising research area which may have translational relevance for understanding the neuro-hormonal bases of human social cognitive abilities.

Dog studies may also hold promise for the development of a new model system for applied pharmaceutical research. These studies may be of particular importance because ASD represents a huge unmet medical need. Namely, this disorder is not only highly prevalent, but, despite great efforts by pharmaceutical companies to develop new treatments, a drug approved for treatment of core symptoms is not yet available. Currently, the almost only way to identify novel compounds is to test those in rodents including idiopathic, environmentally-induced or transgenic models of autism, but the translational value of these rodent models is questionable (as discussed above). Although nonhuman primate models (especially great apes) may represent

an approach with higher translational power, the limited availability of subjects and the ethical concerns pose practical limitations on the possibilities for involvement of primates.

Here we argue that a dog model could be a reasonable alternative solution. While the physiological origin and phenotype of such a model can be established with relative ease, assessing the ability to predict prosocial efficacy of drug candidates in humans is still a challenging issue. The central problem here is the lack of any medication for the core symptoms and thus the lack of a "gold standard" that could be used to verify that the model is able to detect efficacy. The use of compounds that have produced signs of efficacy in humans, such as the neurohormone oxytocin, would help researchers to evaluate the predictive validity of the dog model of ASD.

In summary, this new line of translational research has the potential to contribute to our understanding of the human ASD symptoms and opens the way for the development of a more valid and clinically more relevant animal model system. Whether this approach will prove fruitful remains to be seen, but if yes, then man's best friend, the dog, will become the translational researcher's new best friend.

CONFLICT OF INTEREST

V.R. is a full-time employee of Gedeon Richter Plc. J.T. and B.T. declare no conflict of interest.

RELATED WIREs ARTICLES

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FURTHER READING

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