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To cite this article: Gül Dölen (2015): Autism: Oxytocin, serotonin, and social reward, Social Neuroscience, DOI: 10.1080/17470919.2015.1087875

To link to this article: http://dx.doi.org/10.1080/17470919.2015.1087875

Accepted online: 28 Aug 2015. Published online: 18 Sep 2015.

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Autism: Oxytocin, serotonin, and social reward

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Over 70 years since the first description of the disease, disrupted social behavior remains a core clinical feature of autistic spectrum disorder. The complex etiology of the disorder portends the need for a better understanding of the brain mechanisms that enable social behaviors, particularly those that are relevant to autism which is characterized by a failure to develop peer relationships, difficulty with emotional reciprocity and imitative play, and disrupted language and communication skills. Toward this end, the current review will examine recent progress that has been made toward understanding the neural mechanisms underlying consociate social attachments.

Keywords: Autism; Oxytocin; Serotonin; Reward; Plasticity; Nucleus accumbens; Social.

In his now seminal paper, “Autistic disturbances of affective contact,” published in 1943, Leo Kanner presents case studies of 11 children, and describes a collection of symptoms for which “the ‘pathognomonic,’ fundamental disorder is the children’s inability to relate themselves in the ordinary way to people and situations from the beginning of life” (Kanner, 1943). Over 70 years since this first description of the disease, disrupted social behavior remains a core clinical feature of autistic spectrum disorder (ASD) (Volkmar & McPartland, 2014). Even so, deciphering the etiology and pathophysiology of autism continues to present substantial challenges for genetics, neuroscience, and medicine.

Appreciation of the genetic etiology of autism began with epidemiological studies in the 1970s, revealing the extremely high heritability of the disease (Bailey et al., 1995; Folstein & Rutter, 1977; McQuaid, 1975; Ritvo, Freeman, Mason-Brothers, Mo, & Ritvo, 1985). Shortly thereafter, the first genetic cause of autism, Fragile X (previously called Martin and Bell syndrome) (Richards, Sylvester, & Brooker, 1981), was recognized (August, 1983; Brown et al., 1986), and the causal mutation upstream of the FMR1 gene was identified (Oostra et al., 1990; Verkerk et al., 1991). Since then, over 700 genes have been implicated in the etiology of ASD (https://gene.sfari.org/autdb/HG_Home.do); nevertheless, together, mutations in these genes account for fewer than 25% of cases. Many of these are highly potent rare variant mutations (e.g., Mendelian disorders like Fragile X (August, 1983, 1982; Brown et al., 1986); and structural, or copy number variants (CNVs), like 16p11.2 duplication (Sanders et al., 2011)). Complicating attempts to understand disease etiology, these mutations are incompletely penetrant (only a subset of patients who have the mutation also have autism), and pleiotropic (all known mutations are also causes of intellectual disability, schizophrenia and/or epilepsy) (Sullivan, Daly, & O’Donovan, 2012). More recently, whole exome sequencing studies have identified a handful of de novo, rare variant exonic mutations (e.g., CHD8 which encodes the chromodomain helicase DNA-binding protein 8 (Neale et al., 2012; O’Roak et al., 2012)). Consistent with previous estimates from CNV discovery, these studies suggest that ASD is highly polygenic (i.e., one characteristic is
controlled by two or more genes; estimates for ASD range from 400 to 1000 genes (Sullivan et al., 2012), once again revealing the complexity of ASD etiology.

Evidence for common genetic variation in ASD risk stems largely from genome wide association studies (GWAS) that have examined single nucleotide polymorphisms (SNPs) in a genome wide search for alleles that are more common in affected versus unaffected individuals. Unfortunately, early attempts to use this approach for discovering ASD risk loci have suffered from low sample sizes (McCarroll, Feng, & Hyman, 2014); thus at this time, it is unclear whether common genetic variation accounts for a significant proportion of disease (Sullivan et al., 2012). Nevertheless, modeling studies suggest that ASD etiology cannot be accounted for by supposing rare, but fully penetrant mutations in a small subset of genes (Neale et al., 2012).

It has previously been suggested that the evolutionary persistence of diseases like schizophrenia, which result from the effect of many genes, none of which explains more that 5% of the variance, is best modeled by a “cliff-edged fitness” function (Nesse, 2004). This model predicts that selection pressures push the mean for advantageous mental traits toward a “fitness cliff”; affected individuals are those who have gone over this “fitness cliff,” where the nervous system fails catastrophically (Nesse, 2004). Given the similarities in genetic architecture between ASD and schizophrenia (Sullivan et al., 2012), it is tempting to speculate that the etiology of ASD also follows a cliff-edged fitness function, and that this observation might offer clues for understanding disease pathogenesis. Such clues would be especially welcome in light of growing evidence that many autism risk genes influence neuronal processes non-specifically (e.g., regulation of metabolic activity, immunity, hypomorphic mutations) (Picard et al., 2014; Saxena et al., 2012; Yu et al., 2013) and therefore understanding their function, using, for example, genetic or biochemical pathway analysis (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013; Darnell et al., 2011; Dölen & Bear, 2009; O’Roak et al., 2012; Parikh et al., 2013; Sullivan et al., 2012), will likely offer incomplete insight into the brain mechanisms underlying disease pathogenesis.

The question remains, what might be the advantageous mental trait that selection pressures have pushed to the extreme? To answer this question, returning to Kanner’s original description of the pathognomonic disruption of social interactions is informative:

There is from the start an extreme autistic aloneness that, whenever possible, disregards, ignores, shuts out anything that comes to the child from the outside. . . .

Objects that do not change their appearance and position, that retain their sameness and never threaten to interfere with the child’s aloneness, are readily accepted by the autistic child. He has a good relation to objects, he is interested in them, can play with them happily for hours. . . . The children’s relation to people is altogether different. Every one of the children, upon entering the office, immediately went after blocks, toys or other objects, without paying the least attention to the persons present. It would be wrong to say that they were not aware of the presence of persons. But the people, so long as they left the child alone, figure in about the same manner as did the desk, the bookshelf, or the filing cabinet. . . .

When with other children, he does not play with them. He plays alone while they are around, maintaining no bodily, physiognomic, or verbal contact with them. He does not take part in competitive games. He just is there, and if sometimes he happens to stroll as far as the periphery of a group, he soon removes himself and remains alone. At the same time, he quickly becomes familiar with the names of all the children of the group, may know the color of each child’s hair and other details about each child. (Kanner, 1943)

Perhaps the simplest hypothesis that explains how this “autistic aloneness” develops is that for the autistic child, social interactions are simply not rewarding, or are somehow abnormally rewarding. In the context of this hypothesis, the fitness cliff framework might suppose that evolutionary selection pressures have compelled the reinforcement of social interactions. Indeed, epidemiological studies supporting this view have demonstrated that social interactions are intrinsically important to our health and well-being (Holt-Lunstad, Smith, Layton, & Brayne, 2010). For example, a recent meta-analysis of mortality risk factors has demonstrated that a diminished quality and quantity of social interactions has at least the same magnitude of effect on lifespan as smoking, alcohol, obesity, hypertension and air pollution (Holt-Lunstad et al., 2010).

The ethological significance of social reinforcement is perhaps most evident in the context of reproductive behaviors. For example, lasting social attachment following mating (pair bonding) has evolved under conditions of scarce food resources and low population densities in prairie voles (Microtus ochrogaster) living in the tall grass prairies of the Midwestern United States (Shapiro & Dewsbury, 1990; Young, 2003). It is thought that this social arrangement enhances reproductive success, since nesting in pairs favors the production of high-quality, low-quantity offspring reared by two parents, reduces the risk of not finding a fertile mate, and maximizes utilization of a saturated habitat, where dispersal opportunities are low (Shapiro & Dewsbury,
In contrast, species such as meadow voles (Microtus pennsylvanicus) and montane voles (Microtus montanus) do not display pair bonding behavior and occupy patchy habitats, where dispersal success is more dependent on high-number, low-quality offspring (Shapiro & Dewsbury, 1990; Young, 2003).

Comparative studies in rodent species provided the first clues about the neural mechanisms regulating social attachment. Oxytocin had long been recognized for its ability induce uterine contractions and milk ejection during mammalian parturition and lactation, effects that are mediated by the release of oxytocin into the systemic circulation from axon terminals within posterior pituitary (Dale, 1906; Dölen, 2015; Du Vigneaud, Ressler, Swan, Roberts, & Katsoyannis, 1954; Du Vigneaud, Ressler, & Trippett, 1953; Kam, Aldrich, Grote, Rowe, & Bugbee, 1928; Ott & Scott, 1910). The discovery of oxytocinergic fibers that extended into the brain (Buijs, 1983; Buijs, De Vries, Van Leeuwen, & Swaab, 1983; Buijs, Swaab, Dogterom, & Van Leeuwen, 1978), and electrophysiological effects of oxytocin on brainstem excitatory responses (Morris, Salt, Sofroniew, & Hill, 1980), suggested that the peptide might have an additional role in central nervous system. Shortly thereafter intracerebroventricular (ICV) injection of oxytocin was shown to induce maternal (Pedersen, Ascher, Monroe, & Prange, 1982) and sexual receptivity (lordosis) (Arletti & Bertolini, 1985) behaviors in female rats, although effects on initiation of the spawning reflex in fish had been demonstrated as early as 1955 (Wilhelmi, Pickford, & Sawyer, 1955). The first studies to implicate oxytocin in pair bonding used a combination of comparative receptor autoradiography to demonstrate contrasting patterns of oxytocin receptor expression in montane and prairie vole brains (Insel, Gelhard, & Shapiro, 1991; Insel & Shapiro, 1992; Witt, Carter, & LInsel, 1991), and the partner preference task, a behavioral assay of pair bonding (see also Figure 1), following ICV infusions of oxytocin (Carter, Williams, Witt, & Insel, 1992; Mahalati, Okanoya, Witt, & Carter, 1991).

Further mechanistic studies of pair bonding across vole species highlighted a critical role for oxytocin in the nucleus accumbens (NAc, also called the ventral striatum) (Young, Lim, Gingrich, & Insel, 2001). This brain region is a central node of the mesocorticolimbic reward circuit (Figure 2a), which beginning with the seminal findings of Olds and Milner in 1954 (Olds & Milner, 1954), has been implicated in producing feelings of pleasure for stimuli that are necessary for survival (such as food, water, and sex). Interestingly, every known addictive drug (e.g., cocaine, amphetamine, heroin, opium, and alcohol) activates this reward circuitry and produces, through a variety of mechanisms, an increase in the amount of dopamine (DA) released into the NAc (Lüscher & Malenka, 2011). Based on these observations, and the in vivo firing patterns of DA neurons (in the ventral tegmental area, VTA, and substantia nigra, SN) during reinforcement, most reward-based learning models are founded on the principle that DA serves as the reward signal (Schultz, 2013). Nevertheless, although in vivo microdialysis studies have revealed that DA is released in the NAc of prairie voles during mating (Gingrich, Liu, Cascio, Wang, & Insel, 2000), this effect has also been demonstrated in species that do not form pair bonds (Kohlert, Rowe, & Meisel, 1997; Pflaum, Damsma, Wenkstern, & Fibiger, 1995), so DA alone is unlikely to account for the lasting social attachments seen in pair bonding.

Interestingly, one of the brain regions identified as having species specific increased oxytocin receptor expression in the prairie vole, but not in mice, rats, montane, and meadow voles, which do not form pair bonds, was the NAc (Bielsky & Young, 2004; Insel...
et al., 1991; Ross et al., 2009; Young & Wang, 2004), raising the possibility that oxytocin and DA might work together to enable species specific pair bonding behaviors. The principle cells of the NAc, medium spiny neurons (MSNs), come in two varieties: D1 dopamine receptor expressing (the so-called direct pathway MSNs) and D2 dopamine receptor expressing (indirect pathway MSNs). Furthermore, if paired animals are prevented from mating, partner preference is not observed, unless there is concomitant stimulation of D2 receptors. This D2 agonist-induced partner preference requires activation of oxytocin receptors, and is absent if D2 agonists are administered in the presence of oxytocin receptor antagonists (Gingrich et al., 2000; Liu & Wang, 2003; Wang et al., 1999). The exact nature of this coordination between oxytocin and DA within the NAc of prairie voles remains, at present, unclear; however, ongoing and future electrophysiological studies will likely be informative.

Like conjugal attachments between mated pairs, parental bonding with pups is also thought to have evolved from evolutionary selection pressures determining reproductive success (Insel, 2010). Just prior to parturition, female rats undergo profound behavioral changes that have been correlated with upregulation of oxytocin receptors (Champagne, Diiorio, Sharma, & Meaney, 2001; Francis, Champagne, & Meaney, 2001; Francis, Young, Meaney, & Insel, 2002; Meddle, Bishop, Gkoumassi, Van Leeuwen, & Douglas, 2007; Olazábal & Young, 2006), DA release (Hansen, Bergvall, & Nyiredi, 1993), and c-fos activation (Lonstein, Simmons, Swann, & Stern, 1998) in the NAc. Specifically, while virgin female rats will either avoid or attack pups, just before parturition they begin to build nests, and show interest in pups (as measured by approach and grooming). Drawing from behavioral measures used to assay the rewarding properties of drugs of abuse, studies have also shown that during this time (and for several weeks after delivery), female rats will develop conditioned place preference (CPP) for pup-associated cues (Mattson, Williams, Rosenblatt, & Morrell, 2001), and will lever press for access to pups (Van Hemel, 1973). Although both VTA and the NAc lesions disrupt pup-induced CPP and approach behaviors (Hansen, 1994; Numan & Smith, 1984), surprisingly self-administration behaviors do not require the NAc (and instead are thought to be mediated by the medial preoptic area, MPOA, where oxytocin receptors are also upregulated just before parturition) (Lee, Clancy, & Fleming, 2000).

Although these studies have revealed important neurochemical mechanisms of conjugal and parental attachments, in human patients with autism, attachment to parents and offspring, as well as sexual drive, are spared social behaviors (Mehzabin & Stokes, 2011, 2008; Naber et al., 2007; Rutgers, Bakermans-Kranenburg, Van Ijzendoorn, & Van Berckelaer-Onnes, 2004; Stokes, Newton, & Kaur, 2007). Returning to the fitness cliff model (Nesse, 2004), the specificity of social behaviors that are disrupted in ASD (failure to develop peer relationships, difficulty with emotional reciprocity and imitative play, and disrupted language and communication skills) (Baron-Cohen & Wheelwright, 2003; Bauminger & Kasari, 2000; Bauminger, 2004; Bauminger et al., 2008; Nirit, 2008; Bauminger, Shulman, & Agam, 2003; Izuma, Matsumoto, Camerer, & Adolphs, 2011; Kuhl, Coffey-Corina, Padden, & Dawson, 2005; Leekam & Ramsden, 2006; Liebal, Colombi, Rogers, Warneken, & Tomasello, 2008; Masten et al., 2011; Mundy, Gwaltney, & Henderson, 2010; Naber et al., 2007, 2008; Pierce, Conant, Hazin, Stoner, &
Figure 3. Diagram illustrating the evolution of social living and pair living. In primates social living predated pair living by approximately 30 million years. The two social behaviors are thought to have evolved from distinct selection pressures: social (protection from predation), pair (reproduction, limited resources). mya, million years ago. Source: Shultz et al. (2011).
Figure 4. Social conditioned place preference (sCPP). (a) Diagram illustrating the social conditioned place preference assay, which measures time spent in each chamber, before and after conditioning with social or isolation cues. (b) sCPP following infusion of saline (top) or oxytocin receptor antagonist (bottom) into the nucleus accumbens. (c) sCPP following RbV-cre injection into WT (top) or conditional oxytocin knockout (bottom) the nucleus accumbens. (d) sCPP following AA V-cre injection into WT (top) or conditional oxytocin knockout (bottom) nucleus accumbens. (e) sCPP following infusion of saline (top) or serotonin receptor 1b antagonist (bottom) into the nucleus accumbens. Redrawn from Dölen et al. (2013).
Significantly both the oxytocin and serotonin 1b receptor gene have been identified as autism susceptibility loci (Lerer et al., 2008; Liu et al., 2010; Lucht et al., 2013; Orabona et al., 2009; Wu et al., 2005). Furthermore, plasma oxytocin levels have been correlated with the magnitude of social impairments in autism (Green et al., 2001; Modahl et al., 1998), and serotonin levels have been the most consistently identified serum biomarker of disease (Gabriele, Sacco, & Persico, 2014). Although human studies of the effects of intranasal oxytocin have also widely been used to support the link between oxytocin and autism, in the context of the proposed circuit level specificity of social impairments in ASD, we must exercise caution when interpreting these results, particularly in light of evidence that systemic oxytocin, through its binding at adrenal oxytocin receptors, induces the decrease of circulating cortisol levels (Chiodera & Legros, 1981; Legros, Chiodera, Geenen, Smitz, & von Frencell, 1984; Stachowiak, Macchi, Nussdorfer, & Malendowicz, 1995). These findings indicate that even when social and cognitive effects of intranasal oxytocin are correlated with changes in brain activation patterns, they may be secondary to a systemically mediated attenuation of the stress response (i.e., to social cues, direct gaze) (Ayers, Missig, Schulkin, & Rosen, 2011; Hall, Lightbody, McCarthy, Parker, & Reiss, 2012; Missig, Ayers, Schulkin, & Rosen, 2010; Norman et al., 2012), rather than a primary effect on the central reward circuitry (Churchland & Winkielman, 2012; Dölen, 2015).

Oxytocin is produced in the hypothalamus by two types of neurons: magnocellular and parvocellular. Previously it has been hypothesized that the maternal and conjugal attachments described above are mediated by coordinated release of oxytocin by magnocellular neurons into both the cerebrospinal fluid (paracrine) and the systemic circulation (endocrine) (Dölen, 2015; Ludwig & Leng, 2006). Although conclusive determination of whether consociate
attachments are mediated by oxytocin released synaptically by parvocellular neurons awaits further technology development, the small size (10–15 µm diameter) and anatomical location (medial to the third ventricle) of NAc projecting oxytocin neurons (identified by RbV retrograde tracing and antibody labeling) is suggestive (Dölen, 2015; Dölen et al., 2013).

The implications of circuit level differences between magnocellular and parvocellular oxytocin release mechanisms have been the subject of a recent review (Dölen, 2015), and will not be further discussed here. Nevertheless, in the context of the social impairments characteristic of ASD, it is interesting to note that temporally precise, synapse specific, release of oxytocin by parvocellular neurons on axon terminals in the NAc is perhaps better suited to encode consociate attachments, which develop over years, and are measured and reasoned, requiring demonstrations of reliability, cooperativity, and reciprocal altruism. This difference may be ethologically relevant, since choosing group members involves discrimination between behaviors that benefit the group versus those that do not.

As discussed above, canonical circuit diagrams of brain regions encoding reward have centered on the function of DA released from the VTA into the NAc. Our demonstration of a primary reward that requires serotonin (Dölen et al., 2013), mandates that this diagram be updated to include the dRph (Figure 2b). Since serotonin mediated synaptic plasticity in the NAc occurs in both D1- and D2-receptor-expressing MSN subtypes (Dölen et al., 2013; Mathur et al., 2011), these results suggest that multiple overlapping streams of information are processed by the serotonergic and dopaminergic pathways in parallel. Consistent with this view, recent anatomical tracing experiments have revealed remarkable overlap in the input regions sending projections to the VTA and dRph (Ogawa, Cohen, Hwang, Uchida, & Watabe-Uchida, 2014).

Earlier accounts of the function of serotonin in reward had supposed a supportive role that modulated the effects of DA, in many cases in an opponent fashion (Boureau & Dayan, 2011). More recently, it has been suggested that DA and serotonin may encode reward on different timescales, such that DA encodes acutely reinforcing stimuli, while serotonin is required for delayed gratification rewards (Doya, 2002; Fonseca, Murakami, & Mainen, 2015; Miyazaki, Miyazaki, & Doya, 2012; Tanaka et al., 2004). Such differences in temporal coding could account for discrepant findings concerning serotonin-DA opponency (Boureau & Dayan, 2011), since acute and delayed rewards may, under one circumstance, be opponent (e.g., the acute reward of chocolate cake versus the delayed gratification of successful weight loss) and under different circumstances be congruent (e.g., the acute reward of chocolate cake versus the delayed gratification of successful weight gain).

Paralleling these findings, studies have correlated reinforcement learning with phasic firing of DA neurons in the VTA, and tonic firing of serotonergic neurons in the dRph (Miyazaki et al., 2012). One of the signatures of in vivo DA neuronal firing patterns that has inspired reward-based learning models is the emergence of the so-called “reward prediction error” signal, whereby over time, DA neurons switch from increasing their firing rates at the onset of reward presentation, to increased firing at the onset of the cue that predicts the reward, and decreased firing following the cue, if it fails to predict the reward (e.g., the reward is absent) (Cohen, Haesler, Vong, Lowell, & Uchida, 2012; Schultz, 2013). Recently, a similar signature has also been demonstrated for serotonergic neurons in the dRph, although once again, encoded on a different timescale (Cohen, Amoroso, & Uchida, 2015).

Modern optogenetic technologies have afforded the opportunity to test the sufficiency of serotonergic signals to induce reinforcement learning; however, these studies have yielded conflicting results (Fonseca et al., 2015; Liu et al., 2014; Miyazaki et al., 2014), so at this time, it is unclear whether the firing of serotonin neurons is itself reinforcing. Given the necessity of serotonin for social CPP (Dölen et al., 2013), it is tempting to speculate that compared with serotonin release due to serotonergic neuronal firing, recruitment of serotonin release by oxytocin may initiate a distinct cascade of synaptic events, which might serve as a mechanism for encoding the domain specificity of social reward.

A number of studies in human patients with autism have sought to address the domain specificity or generality of reward impairments in autism. The majority report that patients with autism demonstrate social (domain specific) reward deficits (Chevallier, Huguet, Happé, George, & Conty, 2013; Demurie, Roevers, Baeyens, & Sonuga-Barke, 2011; Stavropoulos & Carver, 2014a), which are correlated with changes in pupillary light responses (Sepeta et al., 2012), event-related potentials (ERPs) (Cox et al., 2015; Stavropoulos & Carver, 2014b), and brain activation patterns measured by fMRI (Abrams et al., 2013; Assaf et al., 2013; Delmonte et al., 2012; Schmitz et al., 2008; Scott-Van Zeeland, Dapretto, Gahremani, Poldrack, & Bookheimer, 2010). Although a handful of studies have demonstrated deficits in monetary (domain general) reward learning in
autism (Dichter et al., 2012; Dichter, Richey, Rittenberg, Sabatino, & Bodfish, 2012; Kohls et al., 2011, 2013, 2014; Neuhaus, Bernier, & Beauchaine, 2015; Richey et al., 2014), others have found either no change (Larson, South, Krauskopf, Clawson, & Crowley, 2011) or increased motivational drive for monetary rewards (Damiano, Alo, Treadway, Bodfish, & Dichter, 2012). Furthermore, when studies have controlled for the lack of saliency of monetary rewards for autistic patients, by using primary rewards such as food or patient salient objects, domain-general deficits have not been detected (Assaf et al., 2013; Cascio et al., 2012). Interestingly, a handful of studies have correlated social reward deficits in autistic patients with changes in activation of the striatum (Assaf et al., 2013; Delmonte et al., 2012; Scott-Van Zeeland et al., 2010), adding to growing evidence in both humans (Loth et al., 2014; Peng et al., 2014; Reiss, Abrams, Greenlaw, Freund, & Denckla, 1995; Ventola et al., 2015) and rodent models (Chen et al., 2011; Dölen et al., 2013; Portmann et al., 2014; Rothwell et al., 2014; Shcheglovitov et al., 2013; Smith et al., 2014; Wang et al., 2008) that the reward circuit might be central to the pathogenesis of disease.

Although the current review has focused on social impairments seen in autism, the disease is also characterized by repetitive behaviors, intense circumscribed interests, and cognitive rigidity (Kanner, 1943; Volkmar & McPartland, 2014). Recent human brain imaging studies suggest that these disruptions are correlated with changes in the development of the dorsal striatum (Kohls, Verys, & Schultz, 2014; Langen et al., 2009, 2014). Interestingly, oxytocin receptor knockout mice have been shown to have cognitive flexibility phenotypes (Sala et al., 2011), and administration of oxytocin into the dorsal striatum of mice has been shown to induce dose-dependent hyperactivity, extensive foraging, increased grooming, and at higher doses, stereotyped scratching, squeaking, and occasional barrel rolling (Delanoy, Dunn, & Tintner, 1978). Given recent localization of rotorod learning phenotypes to the NAc of the NLG3 knockout model of autism (Rothwell et al., 2014), future studies examining the interplay of dorsal and ventral striatum in mediating core symptoms of autism will be informative.

The recognition of so-called “mirror image” structural variants implicated in autism and schizophrenia (whereby deletions predispose to one and duplications predispose to the other disorder (Crespi, 2010; Crespi, Stead, & Elliot, 2010) has mystified geneticists, who have noted, “it is difficult to understand the clinical features of ASD and SCZ as mirror images” (Sullivan et al., 2012). Interestingly, one of the earliest hypotheses concerning autism pathogenesis is that it results from a deficit in theory of mind (ToM) (Baron-Cohen, Leslie, & Frith, 1985; Moran et al., 2011), which is the ability to attribute mindfulness to others (Call & Tomasello, 2008; Denett, 1971; Dziobek et al., 2008; Happé, 1994; Saxe & Kanwisher, 2003). Extending the “mirror image” apposition, schizophrenia might then be best described as “ectopic” ToM, such that inappropriate attribution of mindfulness produces the hallucinations and delusions characteristic of the positive symptoms of disease (Backasch et al., 2013).

It is not clear if, or how, ToM and social reward deficits in autism are related. Some have suggested that social reward deficits are primary, and that ToM deficits follow as “diminished social interest . . . deprive[s] the developing child of social inputs and learning opportunities, which, ultimately, leads to diminished expertise in social cognition” (Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012). On the other hand, future studies examining circuit, synaptic, biochemical mechanisms (for example of parallel processing by oxytocin (Dölen, 2015)) may shed light on how two seemingly disparate behavioral disruptions could arise from a common mechanism. Nevertheless, it must be acknowledged that given the complexity of disease etiology, it is unlikely that any single pathophysiological mechanism will account for all cases of autism. For now, because the brain circuitry subserving reward is largely conserved across humans and mice, the social reward hypothesis provides an opportunity to dissect pathogenic mechanisms of autism, which can be interrelated between autism model mice and human patients with disease, with the ultimate goal of generating mechanism-based therapeutics.

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