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The Autism Diagnosis in Translation: Shared Affect in Children and Mouse Models of ASD

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Abstract

In recent years, there have been significant improvements in assessment and diagnostic procedures for autism spectrum disorders (ASD). Standardized diagnostic instruments have been developed, promoting consistent diagnostic practices among clinicians. For clinical researchers, these instruments have facilitated collaborations across different sites by providing standardized metrics with which to evaluate ASD symptoms. Nevertheless, because ASD remains a diagnosis that is defined on the basis of behavior, there are significant challenges associated with modeling ASD social behaviors in laboratory animals. In order to more effectively study the causes of ASD symptoms and behaviors, there is a need to develop new ways of measuring social behaviors that can be applied to non-human species. Critically, while verbal dialogue between the clinician and patient is integral to clinical diagnoses, it cannot be employed for studies of animal models. However, observations of autistic-like social interactions can be modeled in animals. In this regard, communication between professionals in the clinical and basic sciences is necessary to break down the complex diagnosis into units of social impairment that can be more feasibly measured in different species. This paper presents a discussion between an animal researcher and a clinical psychologist. Using shared affect as an example, we explore potential avenues for increasing the utility of animal models to move us toward a better understanding of the mechanisms underlying social impairments in ASD.

In the absence of molecular biomarkers that can be used to diagnose ASD, current diagnostic tools depend upon clinical assessments of behavior. Research efforts with human subjects have successfully utilized standardized diagnostic instruments, which include clinician interviews with parents and direct observation of the children themselves (Risi et al., 2006). However, because clinical instruments are semi-structured and rely heavily on dynamic social processes and clinical skill, scores from these measures do not necessarily lend themselves directly to experimental investigations into the causes of ASD. Studies of the neurobiology of autism require experimental animal models. Mice are particularly useful, in this regard, for elucidating genetic and toxicological contributions to impairments in social function (Halladay et al., 2009). Behavioral tests have been developed that are relevant to autism (Crawley, 2004, 2007), including measures of repetitive behaviors (Lewis, Tanimura, Lee, & Bodfish, 2007; Moy et al., 2008), social behavior (Brodin, 2007; Lijam et al., 1997; Moretti, Bouwknecht, Teague, Paylor, & Zoghbi, 2005), and vocal communication (Panksepp et al., 2007). Advances also include development of high-throughput measures of mouse sociability that can be used to reliably compare inbred mouse

strains (Moy, et al., 2008; Nadler et al., 2004), as well as measures of social reward (Panksepp & Lahvis, 2007) and empathy (Chen, Panksepp, & Lahvis, 2009; Langford et al., 2006). With continued generation of mouse gene-targeted mice that are directly relevant to genetic linkages in ASD, there remains an urgent need to utilize a full suite of mouse behavioral tests that allows for a *comprehensive* assessment of the spectrum of social difficulties relevant to ASD. Using impairments in shared affect as an example, this paper explores potential avenues for collaboration between clinical and basic scientists, within an amply considered translational framework.

Introduction

Autism spectrum disorders (ASD) are characterized by abnormalities in reciprocal social interaction and communication, and by the presence of restricted and repetitive behaviors (American Psychiatric Association, 1994). During the past 20 years, the increased use of standardized diagnostic instruments has contributed to significant advances in clinical assessment of ASD. These instruments have sought to operationalize general diagnostic concepts, such as ‘abnormalities in social interaction’, by delineating specific behavioral markers of impaired social reciprocity. Based on DSM-IV criteria, the instruments provide information about particular areas of abnormality, such as limited attempts to direct others’ attention through pointing, showing, or commenting, and decreased awareness of and/or responses to other people, such as not responding to one’s name being called, or not seeking out other children. Scores on these measures thus provide a standardized means of organizing and conceptualizing ASD symptoms by ensuring that children across different sites and settings are assessed using similar sets of behavioral criteria (Risi, et al., 2006).

Parent interviews such as the Autism Diagnostic Interview-Revised (Rutter, Le Couteur, & Lord, 2003) and the Diagnostic Interview for Social and Communication Disorders (DISCO: Wing, Leekam, Libby, Gould, & Larcombe, 2002) are designed to gather information about a child’s current and past behaviors that may be relevant to a diagnosis of ASD. The ADI-R includes questions about how a child behaves during various social situations, such as “When your child is excited, how does he share those feelings with you?”, or “How does your child respond when another child approaches him/her?” (ADI-R: Rutter, et al., 2003). Alternatively, tools like the Autism Diagnostic Observation Schedule (ADOS: Lord et al., 2000), the Screening Tool for Autism in Two Year Olds (STAT: Stone, Coonrod, & Ousley, 2000), and the Autism Observation Scale for Infants (AOSI: Bryson, Zwaigenbaum, McDermott, Rombough, & Brian, 2008) provide an opportunity for the clinician to directly observe the child’s social interchanges with an unfamiliar adult, and in some cases, with a parent. In the ADOS, the clinician presents a standard set of activities or questions that are intended to elicit a variety of behaviors and emotional reactions from the child. The clinician then scores his/her observations of these behaviors immediately following the assessment (Gotham, Risi, Pickles, & Lord, 2007; Lord, et al., 2000). In the “Shared Enjoyment” code, for example, the clinician determines a score based on how well the child was able to indicate pleasure during interactions with the examiner. In the case of a young child, a clear indication of sharing enjoyment might be smiling at the examiner and saying “Wow Bubbles” when the examiner blows bubbles. Shared enjoyment that might be observed in an older child could include a visible demonstration of enthusiasm (e.g., smiling, leaning forward in his chair attentively, laughing) as the child relates vacation stories to the examiner. On the other hand, a child would not be rated as sharing enjoyment if he or she exhibited only neutral facial expressions in response to new toys and activities presented by the examiner, or if he responded to the examiner’s attempts to initiate conversation without eye contact and with brief, monotone responses that seemed to indicate a lack of interest.

Standardized diagnostic instruments such as the ADI-R and ADOS are designed to be administered by clinicians trained in ASD diagnostic practices and in coding procedures specific to each of the measures. Unlike symptom checklists that indicate only whether a certain symptom is present or absent, these investigator-based instruments offer clinicians the flexibility to employ their clinical experience to make judgments about symptoms in the context of other behaviors, and to use different clinical skills to gather information needed to derive an overall clinical diagnosis. However, whereas built-in flexibility and reliance on the clinical skills of the examiner are necessary in the context of diagnostic assessment, these features present significant challenges for research aimed at understanding the etiology of ASD. Thus, while these instruments have undoubtedly moved the field toward thinking more specifically about the particular behavioral markers that characterize the ASD phenotype(s), behavioral codes yielded by the instruments' are still relatively broad and do not readily map onto underlying mechanisms (see also Klin, 2008).

Just as the clinical diagnosis of ASD now relies on standardized diagnostic instruments that incorporate a variety of measures of social impairment, evaluations of mouse genetic and toxicological models need to be assessed for an array of distinct social deficits, including sociality, social interaction, social motivation, acoustic communication, and empathy. In the absence of biomarkers that can be used to diagnose ASD, both human and animal researchers are highly dependent upon behavioral observation methodology to characterize their samples. Therefore, in order to more effectively coordinate ASD phenotyping research with basic science investigations into the causes of ASD-related impairments, there is clearly a need to develop and apply novel assessment methods that can be more readily employed to achieve translational research goals (e.g., Klin, Jones, Schultz, Volkmar, & Cohen, 2002).

This paper represents collaboration between a clinical psychologist whose research focuses on assessment of the behavioral phenotypes of children with ASD, and an expert in mouse social behavior who has designed novel behavioral measures of social motivation and communication in mice. We hope that our dialogue can contribute to ongoing efforts to coordinate animal model and clinical research efforts (Lahvis, Alleva, & Scattoni, 2010; Silverman, Yang, Lord, & Crawley, 2010) to identify the underlying causes of ASD.

For the purposes of this discussion, we focus on the issue of impaired shared affect in ASD, which is arguably one of the most central and defining features of the disorder (e.g., Dawson, Hill, Spencer, Galpert, & Watson, 1990; Kanner, 1943; Wing & Gould, 1979; Yirmiya, Kasari, Sigman, & Mundy, 1989). Shared affect can be conceptualized in terms of a "Reciprocity Chain." As with previously proposed organizational structures, such as the Social Information Processing Network (SIPN: Nelson, Leibenluft, McClure, & Pine, 2005), the Reciprocity Chain can be used to translate and extend current ASD diagnostic instruments, with their considerable dependence upon clinician insight, to a useful scientific framework. The Reciprocity Chain isolates shared affect into a linked interplay of four components (see Figure 1).

Measurable features of the reciprocity chain include the expression of emotion by individual A and individual B's ability to physiologically and behaviorally respond to these expressions. Using the Reciprocity Chain as an organizing structure, we will contrast typical human development with ASD, and then examine ways that the broad concept of shared affect might be reduced to elements that can be studied as minimal functional units of behavior in mouse development. Through this process, we hope to draw clear links between relevant human behaviors and potential opportunities to measure those same behaviors in mice.

Section 1: *Homo Sapiens Sapiens*

Shared Affect

A major component of social reciprocity is the ability to share affect with another person (see Markova & Legerstee, 2006). Sharing affect involves using one's own affective expression to draw another individual into a similar emotional experience, such as revealing a concerned facial expression and a softer voice when relating a sad story, or, widening the eyes and directing an expression of surprise to indicate excitement about seeing something for the first time. Perhaps one of the most simplistic examples of sharing affect is social smiling: a person smiles at another person as a simple greeting or to indicate their pleasure in seeing them, which then prompts the other person to smile back in return (e.g., Stern, 1985). Importantly, the key element that differentiates sharing affect from other types of emotional expressions is that shared affect requires that the expression of emotion be directed to another person (Tomasello, Carpenter, Call, Behne, & Moll, 2005).

Individuals frequently express emotions outside of any social context, such as smiling or crying while reading a book alone, cursing in frustration when something breaks, or gesturing in excitement in response to some good news. But *shared* affect is not possible in situations that lack a shared social component. Even if other people are physically present, shared affect cannot be achieved if the individual who experiences an emotion fails to indicate it to another person (as in the second link in the Reciprocity Chain). For example, I might see a kitten jump backwards in surprise from something on the television and laugh to myself. Or, if there is another person in the room with me, I may turn my gaze toward that person and laugh, deliberately and outwardly expressing my emotional experience of the scene. In both scenarios, my emotional experience of the event may be similar (i.e., pleasure, amusement). However, my expression of that emotional experience can only be considered as sharing affect when it is directed toward another person; as if handing them something, like a piece of candy or a toy, which they might enjoy, too.

To achieve a shared affective experience between two individuals, the third link in the Reciprocity Chain must also function. There must be a capacity to respond to the expressions of the individual attempting to share the experience. The person with whom an individual expresses emotion must actually “get it” and express a response in return. The person to whom I direct my amusement of the kitten situation may respond in any number of ways, laughing along with me, in this case sharing amusement, or shaking his head and rolling his eyes, as if to say “You are amused too easily.” Alternatively, the other person may fail to respond to me altogether, in which case the affect is not shared. Whatever the response, it will have consequences for the ensuing social interaction. Thus, shared affect is closely related to social reciprocity. The nature of a person's reciprocal social interactions will be greatly influenced by his/her capacity for shared affect, both in terms of offering to share, as well as in responding to others' attempts to share affect.

Shared Affect in Infants

In typically developing infants, affect sharing begins very early in life and provides one of the first opportunities for infants to interact with other humans (see Markova & Legerstee, 2006). Stern (1985) argued that “affect attunement”, which is exhibited in these earliest interactions (e.g., the parent smiles and the infant smiles back), underlies empathic understanding by providing for mutual appreciation of another person's mental state. Meltzoff similarly argued that neonatal imitation, often demonstrated through matching of facial expressions, serves as a foundation from which infants learn about their own internal states, as well as the internal states of others (see Meltzoff, 2007). Meltzoff theorized that when infants imitate the behaviors of a caregiver, they begin to see the other person as being

“like me.” Viewing another person as “like me” is the beginning of perspective taking, and eventually empathy, because the infant learns to associate internal states with behavior. For example, when a child realizes that crying behavior is associated with an internal state of pain or discomfort, then the child can infer that crying in another person is associated with a negative state of being for that person. Even before children begin consciously engaging in perspective-taking behaviors, however, observations of the earliest interactions between infants and their caregivers seem to suggest that infants are “pre-wired” (perhaps through early imitation skills) to match the affective expressions of the people around them (Feldman, 2007, 2007; Meltzoff, 2007; Trevarthen & Aitken, 2001) .

This drive for affective matching, or “emotional confluence,” may initially act more as a reflex than as a conscious social process. But by 3 months of age, infants engage in reciprocal social exchanges involving coordinated face-to-face interactions that have been argued to provide “critical inputs for the maturation of the social brain” (Feldman, 2007, p. 341). Back and forth emotional interchanges, likened by several authors to a “dance,” rely on the ability of each individual to respond rapidly to changes in the affective expressions of the other. Feldman states “this constant oscillation between momentary miscoordination and interactive repair marks the essence of human dialogue, to which infants are sensitized in their earliest interactions” (Feldman, 2007, p. 341). As typically developing children grow older, they expand their social repertoires to include other behaviors that incorporate the same types of affective sharing, driven perhaps by motivations for emotional confluence first exhibited in infancy (see Trevarthen & Aitken, 2001). Children show their favorite toys, give objects to their caregivers, and point out planes or animals seemingly for the purpose of sharing their interests with others. For most children, it is not enough that *they* are happy about something—these children project their affective states outwardly for individuals around them to see, with an apparent motivation to bring the affective states of others to match their own. If a child sees that her mother smiles in response to her enjoyment of a toy, then this will likely increase the child’s enjoyment of the toy. If, on the other hand, the mother frowns or scolds the child for picking up an expensive crystal bowl, the child may cease her positive emotional display toward the bowl and put it down, with no intention to pick it up again.

In a sense then, a child’s capacity for affective attunement, an ability to sense and respond to the emotions of those around him, allows the child to navigate the social world. Affective attunement might be analogous to the ability of a delivery person to read and respond to road signs while driving a mail truck through the country. Emotional confluence is achieved when the emotional expression of one individual comes to match that of another. The motivation for emotional confluence might be analogous to the motivation to drop a letter off at a specific location. Emotion sharing thus requires a capacity for affective attunement and a motivation for emotional confluence, which occurs as part of a dynamic process of initiations and responses, and which is dependent on contributions from both social partners.

Shared Affect in ASD

Numerous studies have found that children with ASD exhibit deficits in shared affect relative to typically developing children or children with non-ASD developmental disorders (Bishop, Gahagan, & Lord, 2007; Charman et al., 1998; Dawson, et al., 1990; Gotham, Risi, Pickles, & Lord, 2007; Joseph & Tager-Flusberg, 1997; Lord, et al., 2000; Lord, Rutter, & Couteur, 1994). In his original description of the disorder, Kanner described autism as a disorder of “affective contact.” This affective contact was particularly impaired within a social context. Kanner observed that children with autism were “like in a shell,” “happiest when left alone,” acted “as if people weren’t there,” and failed “to develop the usual amount of social awareness” (Kanner, 1943).

More recent clinical studies show that some children who are later diagnosed with ASD exhibit impairments in social responsivity, including abnormalities in affective expression, as early as the end of the first year of life (Maestro et al., 2002; Maestro et al., 2005; Osterling & Dawson, 1994; Ozonoff et al., 2010; Volkmar, Lord, Bailey, Schultz, & Klin, 2004; Zwaigenbaum et al., 2005). Maestro and colleagues (2005) performed retrospective analysis of home videos to identify early abnormalities in affective expression in 40 children who were subsequently diagnosed with ASD. Using the Behavioral Summarized Evaluation (BSE: Barthelemy et al., 1990), the researchers rated the presence of 20 behavioral abnormalities based on video footage taken when the children were between 6 and 12 months old. The most commonly endorsed items involved atypical social initiations and responses, such as “lack of initiative/hypoactivity” (72%), “poor social interaction” (60%), “abnormal eye contact” (47%), “ignores people” (47.5%), and “does not make an effort to communicate using voice and/or words” (40%). This evaluation also included items that were specifically related to emotion regulation, “mood difficulties” (67.5%), and emotion expression, “lack of appropriate facial expressions and gestures” (35%) (Maestro, et al., 2005). Zwaigenbaum and colleagues (2005) have also suggested that early abnormalities in affective expression may be apparent by 12 months of age in children with ASD. Using a prospective longitudinal design of infant siblings of children with autism (who are at much higher risk for ASD than the general population) infants who later received clinical diagnoses of ASD were found to exhibit abnormalities in eye contact, visual tracking, disengagement of visual attention, orienting to name, imitation, social smiling, reactivity, social interest, and sensory-oriented behaviors at 12 months. Thus, although it has not yet been possible to identify clear diagnostic markers that reliably differentiate children with ASD during the first year of life, evidence from both retrospective and prospective infant studies suggest that abnormalities in affective expression, sharing, and responsiveness, are among the earliest behavioral differences in some children who go onto be diagnosed with ASD.

In our own clinical experience, one of the most notable characteristics of interactions with infants later diagnosed with ASD is a lack of affective attunement. Though subtle, and often recognized primarily in retrospect, there is a feeling in interacting with some infants that they are not entirely “present” in the interaction. “Charlie” is a child who was recruited to participate in a study of infant siblings of children with ASD. When he was first evaluated at age 10 months, Charlie was babbling and could say “mama”. He also used a couple of simple gestures, including a sign for “dog” in which he stuck out his tongue and panted. During the 45-minute behavioral assessment, Charlie did many things that typical infants do, including smiling, referencing his mother with eye contact, and playing with toys appropriately. However, there was also something unusual about Charlie’s behavior that was, at first pass, difficult to articulate--something that just didn’t *feel* right. Upon further reflection, the clinicians who worked with Charlie agreed that his behavior, and specifically his affective expression, did not always match with the situation or with the people around him. Though Charlie’s mother often cooed adoringly at Charlie, and the clinician smiled at him when playing peek-a-boo or showing him a new toy, Charlie did not consistently respond to the emotional expressions of his social partners. Because Charlie did not have a temporally responsive emotional expression that was receptive to the expressions of other people in the room, social interactions with him required more work. As opposed to the easy, flowing “social dance” that is typical of many interactions between infants and adults, Charlie’s behavior left the impression that he was not an entirely willing social partner. At two years of age, nearly 14 months after these observations, Charlie was diagnosed with autism.

In the case of infants like Charlie, early deficits in social reciprocity may appear almost as intangibles. Social interactions may seem slightly forced, tenuous, or just “off.” These

intangibles can be captured to some extent with diagnostic instruments and expert clinical judgment, but they have limited value within the constraints of experimental studies. Moreover, systematic empirical research that employs experimental paradigms is needed to take us beyond anecdotes and general descriptions to document the specific quality and developmental course of emerging abnormalities in the ability to share affect. When using a direct observation tool, deficits in shared affect are inferred from a child's social responses within an artificial social stimulus, the examiner. Though the examiner's task is to create and facilitate the social contexts necessary for observing relevant social behaviors, examiner variability in communication style, appearance, cultural background, or gender, or in the ability to convey emotion and modulate energy levels, can all influence the degree to which a child is engaged in the clinical social interaction. Thus, whereas clinical diagnostic tools, including clinical judgment, are required for assessment of shared affect within the ASD diagnostic context, as well as to identify behavioral phenomena most relevant to ASD as a disorder, these same tools do not lend themselves *necessarily* to critical scientific inquiry of the underlying causes of impairments in shared affect. To the extent that assessments of certain ASD-related abnormalities might be conducted without examiners, contributions of examiner variability might be avoided. Further, more automated assessment tools would provide a rich substrate for scientific studies that involve functional brain imaging or animal modeling.

Deconstructing Shared Affect: The Reciprocity Chain

Sharing affect requires individuals to both express emotions and perceive expression by others. The emotions experienced by an individual can be expressed through the meaning of the spoken words, such as "I feel *sad*." Emotions are also routinely conveyed via *how* words are spoken, or prosody (Lahvis, et al., 2010). A flat tone, or lack of frequency modulation, can convey boredom. Variations in frequency and energy levels can indicate excitement or interest. A tremble in a voice can indicate fear. Emotions are also expressed via visual cues, such as facial expressions and body movements, or gesture. For instance, the shape of an individual's eyes can indicate happiness or fear (Darwin, 1872; Ekman, Davidson, & Friesen, 1990; Whalen et al., 2004). Sharing affect requires that the individual detect these auditory and visual cues associated with emotions in another, experience an internal emotion in response to these cues, and then express his/her own emotional experience in a fashion that can be detected by the individual who experienced the initial emotion (Tomasello, et al., 2005). In most cases, shared social interactions are facilitated by different combinations of gesture, facial expression, prosody, and word meaning.

This interplay between the expression and perception of emotional cues, which we call the "Reciprocity Chain," also has a temporal dimension. For individual B within the Reciprocity Chain to perceive that individual A is emotionally responsive to a specific experience, A must demonstrate changes in emotional expression that are related to A's own psychological experience. Meaningful expressions of emotions require that these changing expressions correspond with temporal variations in internal emotional state. Expression and perception of emotional cues require variation in context; they must occur within a dynamic background of emotional expression.

Given the multitude of behavioral elements, dynamic processes, and temporal issues that may impact a child's ability to share affect, approaching the study of shared affect in pieces, rather than as an amorphous diagnostic concept, will be an important step in determining what mechanisms are responsible for "impairments in shared affect" associated with ASD. To this end, the framework of the Reciprocity Chain may prove useful in isolating specific aspects of shared affect that differ in children with ASD and that can be translated into experimental studies of mouse social behavior. Mouse models can then be used to elucidate the genetic and environmental factors that modulate the capacity for shared affect.

Section 2: *Mus musculus*

Genetic utility of the laboratory mouse

Mice are a popular species for genetics research because they have a mammalian brain and a sufficiently short generation time (10 weeks from conception to reproductive maturity) for genetic studies. Mice can be genetically engineered to examine how loss-of-function mutations of specific alleles, such as functional orthologues of allelic variants associated with autism, can influence mouse neurodevelopment and behavior. Gene expression in mice can also be manipulated by RNA interference (Kurian, Bychowski, Forbes-Lorman, Auger, & Auger, 2008) and by insertions of human mutations into the mouse genome (Tabuchi et al., 2007; Turakainen, Saarimäki-Vire, Sinjushina, Partanen, & Savilahti, 2009). Forward genetics, which involves assessments of phenotypic traits against random changes in the genome, can be used to determine how mutations or allelic variants can influence mouse brain development and behavior (Blizard, 1992; Rossant & McKerlie, 2001; Takahashi, Nishi, Ishii, Shiroishi, & Koide, 2008). If a particular mouse strain expresses an anomaly of interest, researchers can then examine the genomic DNA to find the causal mutation, employing strategies that include use of a sequence database for the entire mouse genome (Bult et al., 2004; Hill et al., 2004; Okazaki, et al., 2002).

Gene-targeted mice, such as knockouts, have been generated that carry mutations in genes that have been associated with an autism diagnosis (Autism Genome Project et al., 2007; Barrett et al., 1999; Liu, Paterson, Szatmari, & Autism Genome Project, 2008). Genetic associations include allelic variants of fragile-X (Hagerman, Jackson, Levitas, Rimland, & Braden, 1986; Harris et al., 2008; Rogers, Wehner, & Hagerman, 2001; Zhang, Shen, Ma, Ke, & El Idrissi, 2009), MET tyrosine kinase (Campbell et al., 2006), *mecp2* (Loat et al., 2008), neuroligins (Jamain et al., 2003; Laumonnier et al., 2004), neurexin (Alarcon et al., 2008), and tuberous sclerosis susceptibility complexes (Fryer et al., 1987; Kandt et al., 1992; Wiznitzer, 2004). After allelic variants are found that associate with ASD, gene-targeted mice can be generated and studied to elucidate developmental mechanisms and to evaluate potential treatments. For instance, various gene-targeted mice that have been generated to model Fragile X syndrome (Comery et al., 1997; Spencer, Graham, Yuva-Paylor, Nelson, & Paylor, 2008; Spencer et al., 2006) express deficits in cognitive and social function (Brodin, 2008; Kooy et al., 1996; McNaughton et al., 2008; Spencer, et al., 2008) that are responsive to pharmacological and genetic treatment (de Vrij et al., 2008; Hayashi et al., 2007; Thomas et al., 2011; Veeraragavan et al., 2011; Yan, Rammal, Tranfaglia, & Bauchwitz, 2005). Another substantial advance is that mice of different background strains are being employed to determine how various background genetic influences moderate the pathology of the fragile-X mutation (Spencer et al., 2011). Successes with fragile X mouse models, and several other strains, most notably the BTBR mouse (McFarlane et al., 2008; Moy, et al., 2008; Scattoni, Gandhi, Ricceri, & Crawley, 2008; Yang, Clarke, & Crawley, 2009; Yang, Zhodzishsky, & Crawley, 2007) underscore the importance of mice in autism research. A critical step is to continue to push for more nuanced measures of mouse social ability, including the capacity to express emotion and to respond to emotional expressions of others.

The social aptitude of the laboratory mouse

There are enormous selective pressures on mice to have high levels of social intelligence. Wild mice can live at densities of up to 4,000 mice per acre (Anderson, 1961; DeLong, 1967). Within these dense populations, males and females compete for food and mating opportunities (Wolff, 1985) within highly defined territories and social hierarchies (Autism Genome Project, et al., 2007; Noyes, Barrett, & Taylor, 1982). Males can even moderate social behavior according to the degree of relatedness with mice in adjacent territories

(Hurst & Barnard, 1992). In natural environments, social arrangements fluctuate with season and food availability (Bernerri, Rosenthal, & Rose, 1991). There is a high level of aggressive behavior at high population densities, while gregarious social groups form when the resources for each mouse are more plentiful (Hill, et al., 2004; Krebs, Chitty, Singleton, & Boonstra, 1995).

This web of social arrangements changes with each cohort of juveniles that disperse into or out of the territory, with the ongoing loss of dominant individuals, and with changing food, shelter and mate availability. Inability to respond appropriately to social cues that indicate dominance could result in forced expulsion. Failure to respond to the wriggling (Branchi, Santucci, & Alleva, 2001) and distress (D'Amato, Scalera, Sarli, & Moles, 2005) calls of pups could impair reproduction. Social interaction allows mice to gain knowledge about safe foods to eat (Choleris, Guo, Liu, Mainardi, & Valsecchi, 1997), safe times and places to roam, parasitism within a colony (Kavaliers & Colwell, 1995) and available mates (Holy & Guo, 2005; Wolff, 1985). Abilities to detect distress in another mouse is highly adaptive (for an interesting overview read Chen, Panksepp, et al., 2009). For an essential account of the naturalistic behaviors of feral mice, read Crowcroft (Crowcroft, 1966).

Social factors also play a dominant role in modulation of emotion in mice. This species is among the most highly studied for underlying emotional states. Mice are capable of fear and fear learning (Falls, Carlson, Turner, & Willott, 1997; LeDoux, Iwata, Cicchetti, & Reis, 1988), anxiety (Carola, D'Olimpio, Brunamonti, Mangia, & Renzi, 2002; Hohoff, 2009; Low et al., 2000), depression (Perona et al., 2008; Stone, Lin, & Quartermain, 2008), and anticipation and consumption of rewards (Kelley & Berridge, 2002; Moles, Kieffer, & D'Amato, 2004). These capacities are supported by a highly differentiated limbic anatomy that is common to all mammals (MacLean, 1990) and physiological systems that include dopamine, serotonin, and endogenous opiates (Panksepp, 1998). Drugs of abuse can co-opt natural reward systems (Abarca, Albrecht, & Spanagel, 2002; Bardo & Bevins, 2000; Kelley et al., 2002; Reith & Selmeci, 1992; van Ree, Gerrits, & Vanderschuren, 1999) and pharmaceuticals that are designed to modulate affective states are often developed based upon extensive studies with mouse models (Holsboer, 2001; Hunsberger et al., 2007; Kato, 2006; Pezet & Malcangio, 2004; Rupniak et al., 2001). Importantly, although emotion regulation has been studied extensively in mice, we know relatively little about how mice perceive and respond to the emotions of others, or share affect. To move forward in this field, it would be helpful to reconsider in more depth how emotions are expressed and perceived in ASD. For instance, we need to consider that deficits of shared affect and empathy can be seen in a variety of neuropsychiatric disorders, including psychotic disorders, affective disorders, and personality disorders. What separates ASD from these other disorders is that deficits in social interaction, shared affect and empathy emerge at a very early age. Thus, studies of the expression of shared affect should ideally be conducted *in juvenile mice*. Other aspects of the autism diagnosis should also inform development of measures of social deficits in mouse models.

Section 3: Translation

Expression and Perception of Emotion among Children with ASD

Nonverbal Communication—ASD is associated with abnormalities in several specific nonverbal components of emotion expression, including facial expression, eye gaze, and gesture (American Psychiatric Association, 1994). Facial expression is arguably the most basic means through which humans communicate their emotions to one another, and yet children with ASD have repeatedly been found to exhibit marked abnormalities in this area of nonverbal communication. Both in terms of displaying a limited range of facial expression, and exhibiting facial expressions that are inappropriate to the situation (e.g.,

smiling for no discernable reason), abnormal use of facial expression is a well-established clinical feature of the disorder (Kanner, 1943; Lord, et al., 2000; Lord, et al., 1994). Unfortunately, measures most frequently employed to assess an individual's use of facial expression (i.e., diagnostic measures) do not provide insights into *why* this symptom is observed, which may very well prove critical in understanding ASD-related deficits in shared affect.

Appropriate use of facial expressions in response to a situation, such as smiling in response to another person smiling first, requires that a child first detect the emotional expression of another individual. Thus, abnormalities in observed use of facial expression may be due to a number of different factors that will be important to differentiate (Charman, 2005). Klin and colleagues have employed eye-tracking technology to better understand how individuals with ASD view the world (Klin, Jones, Schultz, Volkmar, & Cohen, 2002). They conducted a series of experiments in which participants watched video clips from Edward Albee's *Who's Afraid of Virginia Woolf* that were selected for high social expressiveness and complexity. Compared to normal controls, individuals with autism were found to focus significantly less time on the eye region of the actors' faces and significantly more time on the mouth, body, and object regions in the film clips. Moreover, within subject variability in the amount of time spent looking at objects was negatively associated with clinical measures of social competence (Klin, et al., 2002). Klin's findings suggest that for some individuals with ASD, abnormal responses to another's emotional state (e.g., deficits in the ability to share affect) may result as much from a lack of *access* to the relevant information, as from misperception or misinterpretation of the information. Whalen has similarly suggested that to the extent that emotions are conveyed by changes in eye shape, individuals with autism may not perceive these changes when they avoid eye gaze (Whalen, et al., 2004). This might explain why children with ASD exhibit abnormalities in perception of emotional facial expressions (e.g., Celani, Battacchi, & Arcidiacono, 1999; Hobson, Ouston, & Lee, 1988).

Another possible explanation for observed abnormalities in shared affect is that a child may notice a change in emotional expression of another individual *yet* fail to express an emotional response that conveys a shared experience. In an experimental investigation of toddlers and preschoolers with autism, developmental disability, or typical development, Scambler, Hepburn, Rutherford, Wehner, & Rogers (2007) reported that 19 out of 26 children with autism were judged to be paying attention when the examiner banged her thumb (e.g., by looking at the examiner in response to her behavior), but only 2 displayed an emotional response (Scambler, et al., 2007). Using a similar response to distress task in a recent prospective longitudinal study of low and high risk infants, Hutman et al. (2010) reported that children who were subsequently diagnosed with ASD exhibited both lower levels of attention and affect in response to the examiner banging his/her thumb compared to the other groups at all time points (12, 18, 24, and 36 months of age). Employing organizational frameworks such as the Reciprocity Chain might help us to better understand the individual components involved in these various behavioral manifestations by forcing us to think beyond the language of diagnostic assessment (e.g., "flat affect"), and moving us instead in the direction of experiments that specifically examine the sequence of events that underlie differences in emotional behavioral output (see also Klin, et al., 2002).

Human Vocalizations—Emotions may also be expressed through verbal communication. If I tell you that I feel angry, despondent, frustrated, defeated, overwhelmed, cagy, indignant, exhilarated, content, proud, or surprised, you know how I feel. In addition to these linguistic approaches to the conveyance of emotional state, emotions are also communicated by how words are emphasized or how pitch oscillates through a statement or monologue. When we study how emotions or intentions are communicated through the acoustic features of speech, such as variations in the pitch of a phrase or sentence, the

duration or loudness of a particular syllable, or the sustained quiver of a fearful voice, we are evaluating the prosodic context of speech. Prosody has a variety of functions that can be delineated. In this discussion, we are particularly interested in *affective prosody*, which refers to the melody of speech that changes with different internal emotional experiences. Also important is *pragmatic prosody*, which is responsive to different social situations. For example, people speak to babies and children with a soft “baby-ease” that they do not use with age-matched peers (Shriberg, Paul, McSweeney, Klin, & Cohen, 2001).

Atypical prosodic expression is a hallmark of autism, although prosody deficits are not universal and when expressed, can be highly variable (McCann, Peppe, Gibbon, O’Hare, & Rutherford, 2007). In the context of the ADOS, children with ASD are more likely to exhibit abnormalities in their modulation of pitch and control of volume compared to typically developing children or those with other types of developmental disabilities (Gotham, et al., 2007; e.g., Lord, et al., 2000).

Children with ASD may produce speech that is monotonic, minimally pitched or energy modulated, such as hypernasality (Paul, Augustyn, Klin, & Volkmar, 2005) or that is amplified in pitch range or even singsong-like (Amorosa, 1992). These qualities may interfere with the communicative effectiveness of the speech, for example by making it difficult to determine whether a sentence is intended as a statement or a question. Moreover, the lack of modulation and repetitive use of specific pitch, duration, or energy changes in the prosodic content may inhibit effective communication of emotion. For example, if a child were to talk in a flat-tone, irrespective of the emotional context or semantic content of the child’s conversation, this lack of variation in vocal expression would negatively impact the child’s ability to inspire an emotional response in the listener (i.e., share affect). Prosodic anomalies in ASD can be subtle, including differences in how long a child pauses before speaking (Heeman, Lunsford, Selfridge, Black, & van Santen, 2010). There can also be abnormal patterns of phrasing and stress placement (Shriberg, et al., 2001). With respect to the reciprocity chain, these features would fall in the category of deficits in the expression of emotions. Children with ASD can also have deficits in the perception of prosody expression, including difficulties interpreting prosodic cues that indicate liking or disliking (McCann, et al., 2007) or that can help disambiguate sentence meaning (Diehl, 2008).

Expression and Detection of Emotional State Change among Mice

Emotion perception is a highly adaptive feature of psychology in the natural environment. For instance, the ability of a wild animal to detect alarm or discomfort in another can prompt vigilance towards threats that would not be directly perceived (Baack & Switzer, 2000; Mateo, 1996). The modality of the distress cues are constrained by the limitations of their natural environments. Wild mice typically experience their environment with only minimal access to lighted areas, sleeping in burrows during the day and foraging at night. As a result, the mouse social environment is less reliant upon visual cues (gestures and facial expressions) than humans. Social stimuli can be mediated via visual cues, but under dark conditions, mice detect each other via vocalizations, odors, and physical contact. In response to painful stimuli, mice can indicate distress via gestures (Langford, et al., 2006), changes in facial features (Langford et al., 2010), vocalizations (Chen, Panksepp, et al., 2009) and olfactory secretions (Rottman & Snowdon, 1972); see below.

Mouse Vocalizations—Mice can emit ultrasonic vocalizations (USVs), which exceed the range of human hearing (15,000 cycles per second (hertz) = 15 kHz). Rat use of USVs to communicate emotions is perhaps best understood, Rats emit higher frequency (50 kHz) USVs when they experience a reward or are in an environment that predicts a reward, and they emit 22 kHz calls under aversive conditions (Burgdorf et al., 2008; Knutson, Burgdorf,

& Panksepp, 1999). These distinct calls elicit different behavioral responses. Rats perform a nose-poke task to hear audio recordings of the higher frequency calls, (Burgdorf, et al., 2008) but do not perform this task for play-backs of lower frequency USVs (Burgdorf, et al., 2008). Immediate early gene expression in the brain shows different patterns of activation when rats hear recordings of high frequency calls versus low frequency calls (Sadananda, Wohr, & Schwarting, 2008). Taken together, these studies demonstrate that different rat vocalizations communicate emotional information, which can be likened to a capacity for affective prosody.

Immediately following birth, pups produce vocalizations that indicate distress. Infant mice emit calls to solicit the dam to retrieve them after they are moved away from the nest (Branchi, Santucci, Vitale, & Alleva, 1998; Fish, Sekinda, Ferrari, Dirks, & Miczek, 2000) and an altogether different call solicits the dam to change her position within the nest. The pup's USVs engender the dam to accommodate the pup, which, in turn, affects call rate. Manipulations of opiates, dopamine, and serotonin physiology change both the rate of mouse pup calls and dam responsiveness to them (D'Amato, et al., 2005; Dastur, McGregor, & Brown, 1999; Fish, et al., 2000; Moles, et al., 2004), consistent with the inference that these calls are emitted during an emotionally distressful experience.

By the time juvenile mice are weaned (PD 21) and before adulthood, they emit a complex repertoire of vocalizations.. One method that reliably produces USVs from juvenile mice entails a brief period of social isolation that is followed by social reunion. When a juvenile mouse is reunited with a familiar juvenile, the isolated mouse follows and sniffs the mouse that has been introduced to its cage. Social approach is generally more vigorous after an extended period of social isolation, particularly if isolation occurs during the dark phase of the light cycle (Panksepp, Wong, Kennedy, & Lahvis, 2008). During the social interactions, high rates of USVs are emitted which can be identified as discrete syllables and classified according to changes in frequency (Panksepp, et al., 2007). These calls vary with the vigor of social approach and vary with strain. Depending upon mouse strain, some aspects of mouse USVs can exhibit highly stereotyped patterns (Panksepp, et al., 2007) or highly unusual call patterns (Scattoni, et al., 2008) that may have relevance to autism.

Studies of vocalizations of adult mice have provided the best evidence for a role of USVs in affective prosody. Mouse vocalizations are responsive to mating access (Barthelemy, Gourbal, Gabrion, & Petit, 2004; Nyby, 1983), the odors of other mice (Branchi, et al., 1998; Elwood, Kennedy, & Blakely, 1990; Nyby et al., 1981), and exposure to drugs, such as amphetamine (Wang, Liang, Burgdorf, Wess, & Yeomans, 2008) and alcohol (Cabral et al., 2006). These studies suggest that mouse vocalizations can indicate differences in emotion states and, in turn, they can have distinct effects on the behaviors of other mice. In theory then, we might capture the *temporal* elements of shared affect between mice by studying how mice respond to the USVs of others.

Within the context of research on shared affect, we can ask how to measure *changes* of a mouse behavior in response to the affective expression of another individual. A simple experimental approach is to employ a modification of a fear-conditioning test to determine how a mouse responds to the distress of another mouse (and see Chen, Rodgers, & McConachie, 2009). In a cue-conditioned fear paradigm, mice can become fearful of an otherwise neutral environmental cue (a tone) after this cue is conditioned by (temporally paired with) the experience of another mouse undergoing momentary distress. A standard fear conditioning procedure entails presenting an animal with a neutral stimulus, such as a 30-second tone, with an aversive stimulus, such as a mild 2-second electrical shock. Upon repeated administration of the paired tone and shock, mice freeze when they hear the tone, in anticipation of the shock.

We used a modification of this paradigm to ask whether two strains of mice that express distinct patterns of social reward (Brodkin, 2007; Panksepp & Lahvis, 2007), could also have discernable differences in the abilities to detect distress in others. In this paradigm, test mice (subjects) observe demonstrator mice (objects) undergo fear conditioning and then we examine whether the subsets freeze in response to the tone when they are placed in the shock chamber. We found that the more social mouse strain (B6) is also capable of acquiring salient, emotional information by observing the distressed demonstrators. The less social strain (BALB) was not able to learn from the object mice.

This enhanced fear learning response in the highly social strain of mice could also be reproduced from 2-second recordings of the vocalizations shock-distressed mice concurrent with hearing the 30-second tone. Thus, like with humans, vocalizations offer a substantial medium for expressing and perceiving emotional information. Within the context of the Social Reciprocity Chain, the mouse strains are distinguished here by the ability to perceive and learn from the distress of others. Notably, the lack of a BALB response could be due to an inherent emotional insensitivity to vocalizations of distressed mice. Control experiments indicated that the BALB mice could hear the calls, since they responded to an environmental cue (the tone) of an overlapping frequency and energy level (approximately 85 dB). One possible explanation for the observed difference between B6 and BALB mice is that the enhanced social motivation of the former strain engenders greater attention towards social cues. Importantly, heart rate deceleration was also expressed in B6, but not BALB mice. The depression of B6 heart rate that accompanies the playbacks of vocalizations from distressed mice also occurs when children detect distress among others (Eisenberg, 2006) allowing us to make inferences to the emotional state of this strain. Within the reciprocity chain, this measure targets the ability of a mouse to respond to the distress expressed by another mouse, but it does not bring us to the final step in our ability to measure shared affect in mice. In this experiment, mouse B observes mouse A in pain (a squeak) associated with a cue (a tone), and then mouse B expresses fear in response to the conditioned cue. However, the expression of pain by mouse A was probably not directed to mouse B, rather the squeak was involuntary reflexive response to the shock. To make this point more clearly, consider alarm calls, which are also emitted by rodents. Prairie dogs use alarm calls to identify different kinds of predatory threats (Fredericksen & Slobodchikoff, 2007; Slobodchikoff, Paseka, A., & Verdolin, 2009). Each call elicits a specific evasion behavior. These kinds of vocalizations are directed toward other rodents, by contrast to the squeaks that are produced by an animal experiencing a shock. Development of a test that measures a *directed expression of emotion* from one mouse to another would be a tremendous advance for autism research. (Fredericksen & Slobodchikoff, 2007; Hodgson, Hofford, Roberts, Wellman, & Eitan, 2010; Hofford, Roberts, Wellman, & Eitan, 2010; Kennedy, Panksepp, Wong, Krause, & Lahvis, 2011; Slobodchikoff, et al., 2009). Such future experiments may require more complex breeding environments that include temporal variations in the availability of rewarding foods and aversive conditions so that mice can designate particular calls to specific affective experiences. Physiological correlates to emotional experiences, such as heart rate and cortisol/corticosterone levels might also be helpful for elucidating shared affective experience. Additionally, attempts to shift focus toward the assessment of *positive* emotion would also be worthwhile, given that the processes implicated in shared positive emotion are likely to differ from those governing more basic “arousal” in response to distress.

Odor—Studies over the last 30 years show that, through odor, mice express information about age, sex, genetic background (Arakawa, Arakawa, Blanchard, & Blanchard, 2007; Eggert, Luszyk, Ferstl, & Muller-Ruchholtz, 1989), degree of kinship (Gilder & Slater, 1978) and parasitic infection (Kavaliers, Choleris, & Pfaff, 2005; Kavaliers & Colwell,

1995). Scent marking behaviors are also highly dependent upon social context (Arakawa, et al., 2007).

Scent marking can engender specific behavioral responses by other mice. For example, scent marking on juvenile mice by females protects them against male aggression (Dixon & Mackintosh, 1976). Males conditioned for low expression of aggression secrete odors in their urine that evoke lower levels of aggressive responses from other males and lower levels of approach from females (Sandnabba, 1986). Mice avoid the urine of individuals stressed by shock (Rottman & Snowden, 1972) or parasitism (Kavaliers & Colwell, 1995) and can even differentially respond to odors that indicate whether another mouse was previously housed in a social or isolate environment (Arakawa, Arakawa, Blanchard, & Blanchard, 2009). In addition to distinct motor responses to odors, mice also express various vocalization patterns when exposed to urine from mice that indicate different social contexts. For example, odors of female mice elicit 70-kHz ultrasonic calls from nearby males (Nyby, Wysocki, Whitney, & Dizinno, 1977).

The excretion of olfactory cues without intent may not suffice as a means to express emotions as defined within the Reciprocity Chain. Just as humans may perspire during experiences of high anxiety, odor itself is likely to be a reflexive response to a particular set of conditions that elicit changes in anatomic physiology. However, the act of scent marking is a behavioral means of disseminating information about individual identity, sex, social dominance, and health (Arakawa, et al., 2009; Arakawa, et al., 2007; Arakawa, Blanchard, Arakawa, Dunlap, & Blanchard, 2008; Ralls, 1971). Thus, odor may serve an important role in the reciprocity chain, and mouse expression (scent marking) and receptivity (differential motor and vocal responses to specific odors) may be helpful for mediating shared affect. At first glance, the slow pace of odor secretion and dissipation may appear to lack face validity with the rapid dynamics of affect sharing inherent in a child's interaction with a parent or clinician. On the other hand, autism is also associated with impairments in the ability to integrate affective signals, perhaps a result of underlying deficits in neural connectivity (Just, Cherkassky, Keller, Kana, & Minshew, 2007; Just, Cherkassky, Keller, & Minshew, 2004; Shapiro & Hertzog, 1991). In this context, olfactory signals might support a particular communication milieu that allows mice to interpret vocalizations or gestures within the more extended timeframe of odorant expression and dissipation. An obstacle within mouse vocalization research is that mice do not express a robust behavioral response to playbacks of recorded vocalizations. Since juvenile mice vocalize mostly during close physical proximity (and maximal olfactory stimulation), it is possible that mouse social interactions require multimodal communication, involving enough cues to assure the mouse that another mouse is present. It is likely that shared affect would transpire within a very close social space.

Interestingly, differences in an individual's level of social motivation may contribute to its ability to perceive the olfactory cues of another mouse. For instance, the capacity of a mouse to respond to olfactory cues that indicate parasitic infection is impaired in targeted disruptions of alleles that moderate social recognition and bonding. Knockout mice that lack functional oxytocin and estrogen receptor genes fail to recognize and avoid parasite-infected mice on the basis of odors, though these mice maintained normal abilities to respond to odor cues of predators (Kavaliers, et al., 2005; Kavaliers & Colwell, 1995). Though perhaps not directly applicable to human interaction, these observations of rodent emotion perception (e.g., in response to odor) could provide new insights into the range of possible factors associated with a person's ability to *perceive* the affective expressions of others.

Gesture and facial expressions

Just as gesture (or posture) and facial expressions are known to play a role in human communication of affect, there is evidence that similar modalities can be indicative of changes in mouse emotional state, such as whether an animal is dominant or subordinate or whether it experiences subjective pain. Mice will show degrees of writhing behavior that directly respond to the concentration of acid injected into the peritoneum (Langford, et al., 2006). When two mice experience different levels of acid, sufficient to engender different degrees of a writhing response, the writhing response of one mouse influences the degree of writhing response of the nearby conspecific (Langford, et al., 2006). Social moderation of writhing response has been interpreted as a form of emotional contagion, analogous to infectious crying among babies (Hoffman, 1975). Tail rattling and various body postures play an important role in communicating aggression or recognition of social status relative to a territory (Crawley, Schleidt, & Contrera, 1975; Scott, 1966). From the perspective of autism research, these behaviors might be considered as gestures that regulate social interactions. There is also recent evidence that mice express a variety of facial patterns in response to pain (Langford, et al., 2010). To the extent that mice can perceive facial patterns, this modality may be relevant to mouse models of autism.

Motivation for Social Interaction—Conditioned place-preference (CPP) tests have provided substantial evidence that mice prefer social encounter to isolation. During a standard CPP experiment, mice are placed into one of two environments that have very distinct qualities. For instance, the beddings of the two environments can be different (one environment contains aspen chips and the other environment is lined with soft paper), or the walls can have either horizontal or vertical lines, or the floors might have circular holes in them or exist as grids of suspended parallel bars. During the conditioning phases of a CPP experiment, the test mouse is housed in one of the two alternate environments. In one of these environments, the mouse is provided with access to a putative reward (e.g. peanut butter, chocolate, cocaine, morphine, another age-matched juvenile mouse). After a period of time, the mouse is placed in the other environment where it does not experience the reward (e.g. lab chow only, saline, social isolation). After repeated exposures to each contingency (environment A and putative reward, environment B without reward) the conditioning phase is completed. The mouse is then placed in a testing structure that contains two chambers, each chamber represents one of the ‘conditioned’ environments, but does not contain the reward. The mouse is allowed free movement between the conditioned environments. If the conditioning stimulus provides a pleasurable experience for the test mouse, then through repeated association with an environment, the mouse chooses to approach that environment. CPP is expressed as the difference between the duration spent in the environment associated with the presence of the putative reward versus time spent in the environment associated with its absence. If the stimulus is rewarding, the mouse should spend more time in the environment associated with the reward.

CPP tests have demonstrated that rodents experience positive affect during different kinds of social encounters, including play (Calcagnetti & Schechter, 1992; Douglas, Varlinskaya, & Spear, 2004), sexual interactions (Camacho, Sandoval, & Paredes, 2004; Jenkins & Becker, 2003), juvenile social interactions (Panksepp & Lahvis, 2007), mother–infant bonding (Mattson & Morrell, 2005; Mattson, Williams, Rosenblatt, & Morrell, 2001) and aggression (Martinez, Guillen-Salazar, Salvador, & Simon, 1995).

Let us transition back for a moment to the ASD diagnosis. A requisite for shared affect among humans is *motivation* for emotional confluence; for the emotional expression of one individual to match that of another. At a more basic level, a motivation for emotional confluence requires a drive to interact with other individuals. CPP tests are thus powerful

tools for assessing the motivations that underlie social interaction, as distinct from propensities for shyness, depression, or attention deficit. Furthermore, it would also be informative to design human experiments that more directly consider the ways in which preferences for certain social stimuli may or may not be related to spontaneous social approach or response behaviors. That is, should a child's social preferences be inferred based on his/her behavioral output, or should preferences for social vs. solitary activities be assessed outside of the context of a complex social interaction (as in the CPP paradigm)? Understanding which particular aspects of the interaction, from preference to motivation to initiation to response, differ in children with ASD will facilitate more successful modeling of these differences in animals.

Physiological Inferences of Emotions in Children and Mouse Models

Physiological correlates of emotion have been described in studies of typically developing infants, but the use of these measures in infant studies of ASD has not yet been extensively explored. Several researchers have argued for the utility of neurobiological measures in the study of emotional responses of young children with ASD (e.g., using event related potentials; see Dawson, Webb, Carver, Panagiotides, & McPartland, 2004; Nelson & McCleery, 2008), but there remains a clear need for more work in this area. In particular, establishing more direct physiological links to infant emotional responses may ultimately prove useful in decreasing our reliance on behavioral measures of shared emotion in ASD. For example, in a study of 5-month old typically developing infants who engaged in face-to-face interactions with a female examiner, infants were found to exhibit increased respiratory sinus arrhythmia (Bult, et al., 2004) and increased theta in several scalp areas in response to a blank face as compared to a smiling face (Bazhenova, Stroganova, Doussard-Roosevelt, Posikera, & Porges, 2007). Field et al. (2007) have also used physiological measures to document differences in the emotional responses of infants born to depressed or non-depressed mothers. Newborn infants born to non-depressed mothers show decreased sucking behaviors and heart rate when exposed to crying of other infants, whereas newborns of depressed mothers do not exhibit any change in sucking behaviors or heart rate. Like behavioral expressions, these physiological parameters are only correlates of emotional states. Nevertheless, they could be valuable for bridging the gaps between the shared affect behaviors we observe and the mechanisms that underlie those observations. Further, these parameters may be very useful for assessments of mice that carry targeted alleles orthologous to the allelic variants associated with autism. Continued exploration of the use of technologies that can be employed in real time alongside behavioral observations of humans and mice will also improve interpretations of behavioral events that transpire across the Reciprocity Chain.

Conclusion

Recently developed standardized diagnostic instruments have led to more coordinated research efforts on ASD in children and adults across multiple sites and samples, but these batteries have not been systematically translated to assess key symptoms and characteristics of ASD in model animal species, such as mice. A core feature of the autism diagnosis is the inability to share affect, which can be delineated within a rich theoretical framework. The expression of shared affect is the culmination of several discrete psychological functions, including a motivation for emotional confluence and the ability to perceive and respond to a change in emotional expression by another individual, via changes in prosody, gesture, or facial expressions.

Indeed, studies of mouse social interactions have provided insight to the genetic and anatomic contributions to ASD-relevant social deficits. Mouse models of ASD can have

deficits in the ability to regulate social interactions and in vocal and olfactory communication . (McFarlane, et al., 2008; Moy, et al., 2008; Scattoni, et al., 2008).

In some cases, emotional information is transmitted, but the cues relevant to social communication are unknown. To assess expression of emotion, we may gain insight from assessments of the social responses of a reference mouse toward a test mouse relevant to developmental disability. To the best of our knowledge, there is only one report of this approach in the literature, in which a reference mouse shows reduced social interaction toward a gene-targeted model of Rett Syndrome (Shahbazian et al., 2002). Analogous results have been identified in drug research. Adolescent B6 mice differentially respond to stimulus mice exposed to low doses of morphine versus mice injected with saline (Kennedy, et al., 2011). Further, these social interactions can sensitize the reference mice to future exposures to morphine (CITE). Again, the social cues are important, but not yet delineated.

A deeper question still, is whether mice can intentionally share affect with their conspecifics. To this end, experiments may involve more advanced technologies. For instance, it would be highly informative to know how the USV repertoire of an individual mouse (B) changes *in real time* with the behavior or vocalization pattern emitted by another mouse (A). This question might be resolved by capitalizing on technologies developed for bat vocalization research; telemetric microphones that can be placed on bats and can record the calls of individuals (Hiryu, Bates, Simmons, & Riquimaroux, 2010; Hiryu, Shiori, Hosokawa, Riquimaroux, & Watanabe, 2008). At the very least, mouse models of autism might be examined for their ability for turn-taking with their vocalizations.

To direct these specifics head on, we need combined efforts by experts in both clinical diagnosis and mouse behavioral research, as we have attempted to do here. We offer a set of specific suggestions that can be implemented simultaneously in both clinical observation and experimental research. We need to implement measures that incorporate objective scales (e.g., biological and physiological correlates of emotion) that can be used as proxies to examine aspects of 'shared affect' in mouse studies. In this regard, the Reciprocity Chain might provide a common ground that helps us to translate clinical and bench research. The concept of a Reciprocity Chain facilitates access to an extensive body of research that extends well over 40 years on mouse auditory and olfactory communication, empathy, and social learning, within the contexts of equally substantial theoretical and physiological frameworks of mouse motivational systems. Formal use of a common framework would facilitate translation of human and animal studies relevant to autism research.

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Figure 1.
The Reciprocity Chain